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Draft Criteria Document for 1,2-Dichloroethane

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FEBRUARY 1984

HEALTH EFFECTS BRANCH
CRITERIA AND STANDARDS DIVISION
OFFICE OF DRINKING WATER
U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

This document summarizes the health effects of 1,2-Dichloroethane. Topics include: General Information and Properties; Human Exposure: Pharmacokinetics; Health Effects in Animals and Humans; Mechanisms of Toxicity; Risk Assessment and Quantification of Toxicological Effects.

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I. Summary

1,2-Dichloroethane (ethylene dichloride, EDC, 1,2-DCE) is the largest volume chlorinated organic chemical in production, and thus has the potential for significiant environmental pollution. Its use as an intermediate in the manufacture of vinyl chloride constitutes the largest volume of usage, but the many dispersive uses probably contribute more significantly to human exposure. These dispersive uses include fumigating stored grain, extracting oil from seeds, manufacturing paints, coatings and adhesives, cleaning textiles, cleaning polyvinyl processing equipment and as a solvent for processing pharmaceutical products and animal fats.

Despite its widespread use, little 1,2-DCE has been detected in air, food or water except near point emission sources. Most authorities consider that air is the principal route of exposure, although environmental sampling indicates that average exposure is minimal. Fugitive emissions from industry and miscellaneous consumer applications of products containing 1,2-DCE are more likely to be the major sources of exposure to humans in non-industrial settings.

1,2-DCE exhibits a high degree of toxicity in animals and is a mutagen as well as an animal carcinogen. Most studies reported in the literature are inhalation studies; very little has been reported on ingestion toxicity other than carcinogenicity. Also, the exposure dose levels in the inhalation studies have invariably been in a range not normally encountered in the environment. Virtually nothing is known of the more subtle toxicology of very low chronic exposure to 1,2-DCE. Numerous instances of human toxicity have been recorded, resulting from industrial exposures or accidental or deliberate ingestion.

No definitive studies have been reported on the nature or the extent of 1,2-DCE metabolism in humans after exposure. On the basis of limited studies on animals, metabolites which have been identified *in vivo* in mice and rats or in liver and kidney crude enzyme systems *in vitro* are (1) 2-chloroethanol, (2) 2-chloroacetic acid, (3) S-carboxymethylcysteine, (4) thiodiacetic acid, (5) glycolic acid, (6) oxalic acid, (7) carbon dioxide and (8) S,S-ethylene-bis-cysteine.

The National Academy of Sciences (NAS) Safe Drinking Water Committee and EPA's Carcinogen Assessment Group (CAG) have calculated projected incremental excess cancer risks associated with the consumption of 1,2-DCE via drinking water by mathematical extrapolation from high dose animal studies using the linear, non-threshold multi-stage model (NAS, 1979; Anderson, 1983). A range of 1,2-dichloroethane concentrations was computed that would be estimated to increase the risk of one excess cancer case per million (10^6), per hundred thousand (10^5) or per ten thousand (10^4) people over a 70-year lifetime, assuming daily consumption at the stated exposure level. The Academy estimated, at the upper 95% confidence limit, that consuming two liters of 1,2-DCE contaminated water per day over a lifetime having a 1,2-dichloroethane concentration of 70 ug/l, 7ug/l or 0.7 ug/l would result in one excess cancer per 10,000, 100,000 or 1,000,000 people exposed, respectively. Using the CAG approach, it can be estimated at the upper 95% confidence limit that consuming two liters of contaminated water per day over a lifetime having a 1,2-dichloroethane concentration of 95 ug/l, 9.5 ug/l, 9.5 ug/l or 0.95 ug/l would result in one excess cancer per 10,000 100,000 or 1,000,000 people exposed, respectively.

Using methodology described in detail elsewhere, the EPA's Carcinogen Assessment Group also has calculated estimated excess cancer risk rates associated with 1,2-dichloroethane in ambient water, extrapolating from data obtained in the NTP bioassay in male rats (increased incidence of hemangiosarcomas)(U.S. EPA, 1980; NCI,1978). CAG employed the linear non-threshold model to estimate the upper bound 95% confidence limit of the excess cancer rate that would occur at a specific exposure level for a 70 kg adult, ingesting 2 liters of water and 6.5 g of fish and seafood/day ("fish factor"), over a 70-year lifespan.

These estimates are summarized in Table I-1.

TABLE I-1

Drinking Water Concentrations and Associated Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l[a])		
	CAG[b]	CAG[c]	NAS[d]
10^{-4}	94.0	59.9	70.0
10^{-5}	9.4	6.0	7.0
10^{-6}	0.94	0.6	0.7

---

[a] Assumes the consumption of two liters of water per day, except for CAG[b] which also included "fish factor"; upper 95% confidence limit

[b] (U.S.EPA,1980)

[c] (Anderson, 1983)

[d] (NAS, 1977;1980)

II. General Information and Properties

1,2-Dichloroethane, the first chlorinated hydrocarbon described in the chemical literature, was produced initially by Dutch chemists in 1795 (Hardie, 1964). For more than a century, little commercial use of the compound occurred. By 1970, however, such strong demand existed that 1,2-dichloroethane was manufactured in greater tonnage than any other chlorinated organic compound (Rothon, 1972). In 1975, 1,2-dichloroethane was the sixteenth highest-volume chemical produced in the United States (Hawley, 1977). Previously regarded by some investigators as an irritating but relatively non-toxic liquid (Rothon, 1972), 1,2-dichloroethane is now recognized as a highly toxic material and a potential human carcinogen and mutagen (Fishbein, 1976).

PHYSICAL PROPERTIES

1,2-Dichloroethane is a colorless, oily liquid that has a sweet taste and an odor like chloroform (Hawley, 1977). It is appreciably volatile, evaporating at a rate which is 0.788 times that of carbon tetrachloride or gasoline (Whitney, 1961). Air saturated with 1,2-dichloroethane contains 350 g/m^3 at 20°C and 537 g/m^3 at 30°C. Its solubility in water is 9 g/l at 20°C. (Irish, 1963). 1,2-Dichloroethane is completely miscible with ethanol, chloroform, ethyl ether and octanol (Windholtz, 1976). The log of the partition coefficient (log P) of 1,2-dichloroethane between octanol and water is 1.48 (Radding et al., 1977).

1,2-Dichloroethene forms an azeotrope with water which distills at 71.9°C under a pressure of 1 atm. The binary azeotrope contains 19.5% water. Fourteen other binary azeotropes are known (Mitten et al., 1970). A ternary azeotrope containing 78% 1,2-dichloroethane, 17% ethanol, and 5% water boils at 66.7°C.

1,2-Dichloroethane is a good solvent for fats, greases, waxes, unvulcanized rubber, resins and many other organic compounds (Hardie, 1964); however, its usefulness as a solvent for cellulose ethers and esters is enhanced greatly by the addition of methanol, ethanol or their acetates (Mitten et al., 1970).

Other physical properties are listed in Table II-1.

CHEMICAL PROPERTIES

Dry 1,2-dichloroethane is stable at ambient temperature but decomposes slowly in the presence of air, moisture and light, forming hydrochloric acid and other corrosive products. The decomposing liquid, which becomes darker in color and progressively acidic, can corrode iron or steel containers. This deleterious reaction is completely inhibited by small concentrations of alkylamines (Hardie, 1964).

TABLE II-1

Physical Properties of 1,2-Dichloroethane

Molecular weight	98.96
Density at 20°C	1.2351
Melting point, °C	-35.36
Boiling point, °C	83.47
Index of refraction at 20°C	1.4448
Vapor pressure, torr	
At 10.0°C	40
At 29.4°C	100
Solubility in water, ppm	
At 20°C	8,690
At 30°C	9,200
Vapor density (air = 1)	3.42
Flash point, closed cup, °C	13
Ignition temperature, °C	413
Viscosity at 20°C, cP	0.840
Conversion factors at 25°C and 760 torr	1 mg/liter = 1 g/m^3 = 247 ppm 1 ppm = 4.05 mg/m^3 = 405 ug/liter

Source: Verschueren, 1977; Weast, 1977.

Both chlorine atoms in 1,2-dichloroethane are reactive and can be replaced by other substituents. This bifunctional nature of 1,2-dichloroethane makes it useful in the manufacture of condensation polymers (Rothon, 1972). Hydrolysis, with slightly acidulated water at 160°C to 175°C and 15 atm pressure or with aqueous alkali at 140°C to 250°C and 40 atm pressure, yields ethylene glycol, $HOCH_2CH_2OH$. At 120°C, addition of ammonia under pressure yields ethylenediamine, $H_2NCH_2CH_2NH_2$. 1,1,2-Trichloroethane, $CH_2ClCHCl_2$, and other higher chloroethanes are formed by chlorinating 1,2-dichloroethane at 50°C in light from a mercury vapor lamp. 1,2-Dichloroethane reacts with sodium polysulfide to form polyethylene tetrasulfide and with fuming sulfuric acid to give 2-chloroethylsulfuryl chloride, $CH_2ClCH_2OSO_2Cl$. With Friedel-Crafts catalysis, both chlorine atoms in 1,2-DCE can be replaced with aromatic ring compounds; for example, with benzene, diphenylethane, $C_6H_5CH_2C_6H_5$, is formed (Hardie, 1964).

CONTAMINANTS AND CHARACTERISTICS OF THE COMMERCIAL PRODUCT

Commercial 1,2-dichloroethane is usually technical grade material that is 97% to 99% pure. Common commercial specifications for this product include: (1) free from suspended matter and sediment; (2) color, to pass test; (3) distillation range, 82.5°C to 84.5°C at 760 torr; (4) specific gravity at 20°C, 1.253 to 1.257; and (5) maximum activity, as HCl, 0.005%. Most commercial products contain about 0.1%

by weight alkylamine to inhibit spontaneous decomposition (Mitten et al., 1970). Uninhibited or impure 1,2-dichloroethane may contain chlorine or hydrogren chloride that can corrode iron or steel containers normally used to store or transport technical grade material. Technical grade 1,2-dichloroethane is a severe fire hazard and a moderate explosion hazard, but spontaneous heating is not a problem. When subjected to excessive heating, such as during a disaster, technical grade 1,2-dichloroethane may decompose, releasing hydrogen chloride and phosgene, both of which are highly toxic (Sax, 1975).

III. PHARMACOKINETICS

General

Very little is known of the tissue distribution, accumulation, metabolism or biological half-life of dichloroethane in the human after acute or chronic vapor inhalation, the most common form of exposure. Few data are available on metabolism after ingestion. From the few quantitative studies in mice after intraperitoneal administration, a major route of excretion of unchanged dichloroethane is via the lungs, but the compound is readily and extensively metabolized principally by the liver and to an unknown extent by other tissues. Renal excretion is the important route of elimination of end degradation products. Detailed information on the mammalian biotransformation intermediates is not available, although some principal metabolites have been identified and several pathways of metabolism proposed. The importance of greater knowledge of the biochemical mechanisms and pathways of metabolism rest in the growing awareness that the intermediate metabolites of dichloroethane probably are responsible for the tissue and organ toxicities of the compound and also for its carcinogenic potential. 1,2-Dichloroethane itself appears to be only a weak mutagen, but at least four postulated metabolites, namely, chloroacetaldehyde, chloroethanol, S-chloroethylglutathione, S-chloroethylcysteine, have been shown to be strong mutagens in bacterial test systems. In addition, direct covalent binding of as yet unidentified highly reactive metabolites to DNA and microsomal protein has been noted. Further research on the pharmacokinetics and metabolism of dichloroethane is strongly indicated, particularly with respect to low chronic exposures by inhalation or ingestion, if rational and intelligent assessment of the hazard potential of 1,2-DCE is to be made.

ABSORPTION AND DISTRIBUTION

Inhalation of 1,2-dichloroethane vapor in air is the common route of exposure at work sites where this compound is manufactured or used. Accidental or intentional ingestion of 1,2-dichloroethane is considered to be uncommon. Skin absorption occurs but is negligible in most industrial vapor exposure situations, although absorption may be significant by this route with direct liquid contact (Irish, 1963).

No systematic studies of absorption, distribution or excretion of 1,2-dichloroethane by humans have been reported. However, once inhaled or ingested, 1,2-dichloroethane can be expected to be distributed into virtually all body tissues. The compound is appreciably soluble in water and very soluble in lipid with partition coefficients at 25°C for olive oil/gas and blood serum/gas of 164 and 30, respectively (Morgan et al., 1972). As expected from its general anesthetic properties in animals, 1,2-dichloroethane readily passes the blood/brain barrier. Distribution is known to occur also into milk (Urosov, 1953) and across the placental barrier into the fetus (Vozovaya, 1975, 1976, 1977).

Pulmonary excretion of dichloroethane, as with other halogenated hydrocarbons, is undoubtedly the major route of elimination of unmetabolized dichloroethane following exposure. Urosov (1953) reported that women exposed to about 15.5 ppm demonstrated initial concentrations in exhaled air of 14.5 ppm. The breath concentration declined to about 3 ppm 18 hours after exposure was terminated. Similar observations have been made in animals (monkey, dog, cat, rabbit, rat and guinea pig) in early investigations of the anesthetic properties and toxicity of dichloroethane (Kistler and Luckhardt, 1929; Lehman and Schmidt-Kehl, 1936; Heppel et al., 1945). Yllner (1971a) found that up to 45 percent of an intraperitoneal dose of 1,2-dichloroethane (0.17 mg/kg) was recovered unchanged and excreted in the urine, indicating that extensive biotransformation occurs in mice. The percentage recovered in exhaled air unchanged increased with the dose suggesting a limited capacity for biotransformation (Table III-1).

TABLE III-1

Percent Distribution of Radioactivity Excreted (48-hr) by Mice Receiving 1,2-Dichloroethane-^{14}C*

	Dose (g/kg)			
	0.05	0.10	0.14	0.17
$^{14}CO_2$ (exhaled air)	13	8	4	5
Dichloroethane (exhaled air)	11	21	46	45
Urinary metabolites	73	70	48	50

*Adapted from Yllner (1971b)

The accumulation of 1,2-dichloroethane in the milk of cows fed with fumigated grain was studied by Sykes and Klein (1957). These researchers administered the 1,2-dichloroethane as a corn oil solution in sealed gelatin capsules. Two cows received the equivalent of 100 ppm in 7 kg of grain concentrate daily. Two other cows were fed the equivalent of 500 ppm for the first 10 days , then 1000 ppm for an additional 12 days. A fifth cow served as a control. Seven milk samples were analyzed between the 3rd and 22nd days of the experiment. The concentration of 1,2-dichloroethane in the control sample varied from 0.0 to 0.10 ppm, with a mean of 0.06 ppm. The milk of cows receiving 100 ppm daily contained from 0.10 to 0.29 ppm 1,2-DCE, reaching a peak on the 5th day, then declining to the minimum. The milk of cows receiving the higher dose of 1,2-dichloroethane contained from 0.18 to 0.45 ppm. The highest concentration was reached on the 9th day, after which a slow decline was observed. No reduction in appetite or milk production occurred during the experiment. Sykes and Klein (1957) also considered the possibility that 1,2-dichloroethane is metabolized by cows to a non-volatile organic chloride, but they were unable to verify the presence of chloride in milk from a cow fed 1000 ppm 1,2-dichloroethane for 12 days.

METABOLISM AND DISPOSITION

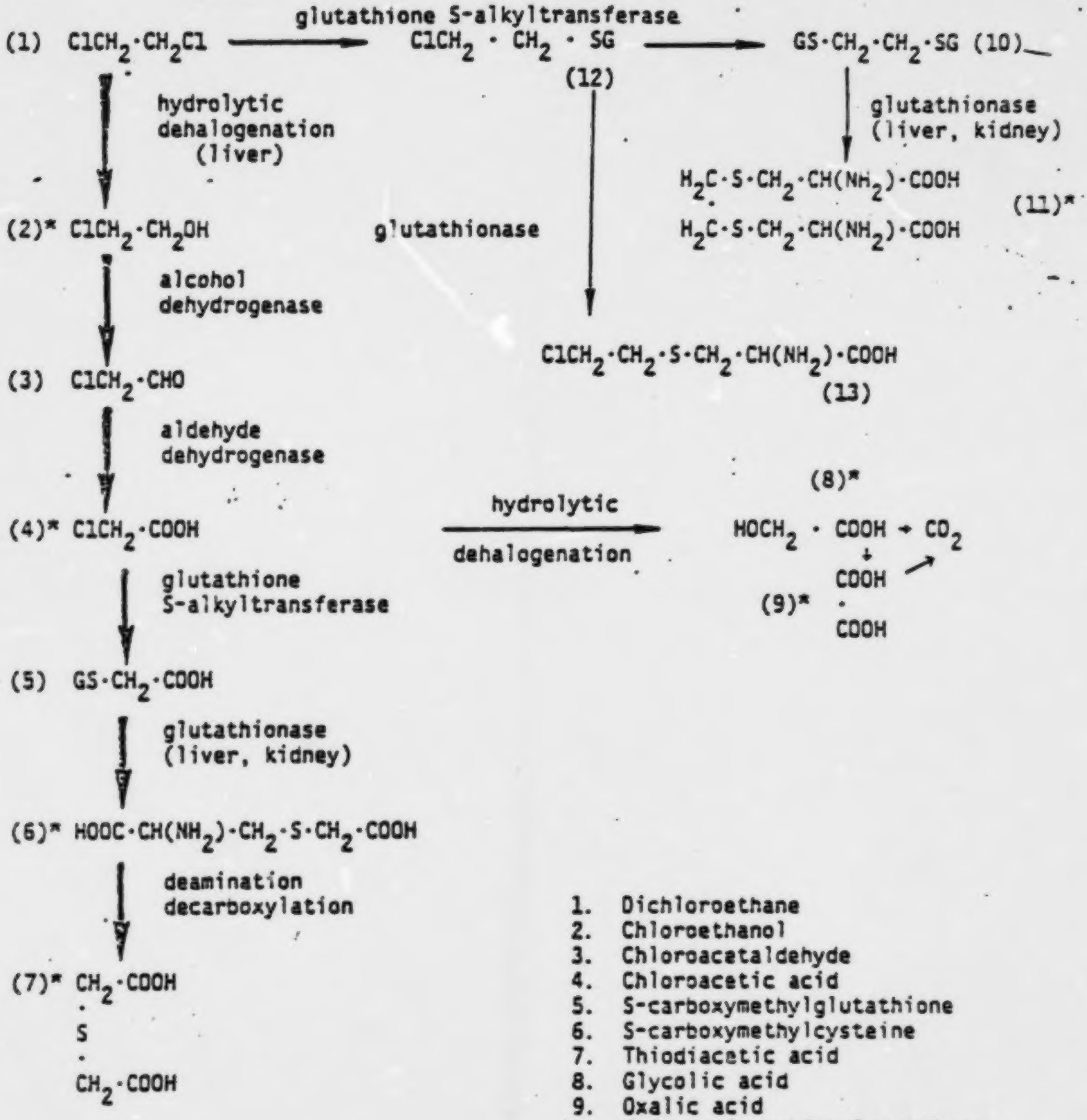
Until recently, almost all of the volatile haloalkanes, particularly those used as anesthetics, were considered to be biologically inert substances eliminated from the body via the lungs without significant alteration. Considerable evidence is now available to show that many of the volatile industrial solvents as well as the most commonly used anesthetics are metabolized appreciably in vivo (Van Dyke and Chenoweth, 1965; Cohen, 1971; Cascorbi et al., 1972). Some of the most significant questions to be answered deal with the possible toxic effects produced by metabolites of the haloalkanes on liver and kidney as well as their mutagenic, teratogenic and carcinogenic potential.

No definitive studies have been reported on the nature or the extent of dichloroethane metabolism after human exposure. Bryzkin (1945) reported that dichloroethane underwent rapid transformation to an "organic chloride" in patients who subsequently died after ingesting 150 to 200 ml; dichloroethane itself was not, however, found in tissues at autopsy. Current information on mammalian metabolism of 1,2-dichloroethane derives from only a few animal studies. Figure III-1 shows the probable mammalian biotransformation of this haloalkane as determined from these studies. Metabolites which have been identified in vivo in mice and rats, or in liver and kidney tissue crude enzyme systems in vitro are: (1) 1-chloroethanol, (2) 2-chloroacetic acid, (3) S-carboxymethylcysteine, (4) thiodiacetic acid, (5) glycolic acid, (6) oxalic acid, (7) carbon dioxide, (8) S,S-ethylene-bis-cysteine.

Main Pathway

The principal pathway of metabolism as shown in Figure III-1 and determined by Yllner (1971a, b) in mice, involves

Figure 3. Postulated Pathways of Biotransformation of Dichloroethane (based on a review of available studies)


(1) ClCH₂·CH₂Cl
glutathione S-alkyltransferase
ClCH₂ · CH₂ · SG
(12)
GS·CH₂·CH₂·SG (10)
hydrolytic dehalogenation (liver)
glutathionase (liver, kidney)
H₂C·S·CH₂·CH(NH₂)·COOH
H₂C·S·CH₂·CH(NH₂)·COOH
(11)*
(2)* ClCH₂·CH₂OH
glutathionase
alcohol dehydrogenase
ClCH₂·CH₂·S·CH₂·CH(NH₂)·COOH
(13)
(3) ClCH₂·CHO
aldehyde dehydrogenase
(8)*
(4)* ClCH₂·COOH
hydrolytic
dehalogenation
HOCH₂ · COOH → CO₂
COOH
(9)*
COOH
glutathione S-alkyltransferase
(5) GS·CH₂·COOH
glutathionase (liver, kidney)
(6)* HOOC·CH(NH₂)·CH₂·S·CH₂·COOH
deamination decarboxylation
(7)* CH₂·COOH
S
CH₂·COOH

1. Dichloroethane
2. Chloroethanol
3. Chloroacetaldehyde
4. Chloroacetic acid
5. S-carboxymethylglutathione
6. S-carboxymethylcysteine
7. Thiodiacetic acid
8. Glycolic acid
9. Oxalic acid
10. S,S-ethylene-bis-glutathione
11. S,S-ethylene-bis-cysteine
12. S-chloroethylglutathione
13. S-chloroethylcysteine

- - - - - - - - → alternative pathway (Johnson, 1966, 1967)

* metabolites which have been identified

an initial hydrolytic dehalogenation to 2-chloroethanol, conversion by alcohol and aldehyde dehydrogenases to monochloroacetic acid (a major urinary metabolite), with further dehalogenation by enzymatic interaction of monochloroacetate with glutathione or cysteine to yield S-carboxymethylcysteine and finally thiodiacetic acid. Yllner administered dichloroethane-^{14}C and chloroacetate-^{14}C intraperitoneally to mice and determined the metabolites in urine and exhaled air. The results of his experiments are summarized in Table III-1 and III-2. Some 11 to 46 percent (increasing with dose; Table III-1) of the injected dichloroethane was excreted via the lungs unchanged; 5 to 13 percent was metabolized to carbon dioxide and water, and the remainder, 50 to 73 percent of the dose, was excreted as urinary metabolites. Table III-2 lists the metabolites identified in urine after dichloroethane and chloroacetic acid administration.

Yllner (1971a, b) proposed that the degradation of 1,2-dichloroethane to 2-chloroacetic acid involves a primary reacton in which chlorine is removed from one of the carbon atoms (hydrolytic dehalogenation) to yield 2-chloroethanol. As evidence for this reaction, he found chloroethanol to be a metabolite (minor) in the urine (Table III-2). Kokarovtseva and Kiseleva (1978) also have identified chloroethanol in the blood and in liver tissue of rats within one hour and four 24-48 hours after oral administration of dichloroethane (750 mg/kg). Heppel and Porterfield (1948) obtained an enzyme preparation from rat liver capable of hydrolyzing the

TABLE III-2

Percent Distribution of Radioactivity Excreted (48-hr) as Urinary Metabolites by Mice Receiving 1,2-Dichloroethane-^{14}C*

Metabolite	After dichloroethane (0.17 g/kg)	After chloroacetate (0.10 g/kg)
Chloroacetic acid	16	13
2-chloroethanol	0.3	--
S-carboxymethylcysteine	45	39
Conjugated S-carboxymethylcysteine	3	3
Thiodiacetic acid	33	37
S,S-ethylene-bis-cysteine	0.9	--
Glycolic acid	--	4
Oxalic acid	--	0.2

*Adapted from Yllner (1971a, b)

carbon-halogen bonds of chloro-derivatives of methane and ethane. Dichloroethane was a substrate for this enzyme, although the reaction product was not specifically identified as chloroethanol. Furthermore, from a quantum chemical study of the metabolism of a series of chlorinated ethane anesthetics, Loew et al. (1973) concluded on theoretical grounds that the initial metabolic reaction is a hydrolytic fission of a carbon-chlorine bond with the formation of alcohols. The enzyme or enzyme system for this primary reaction has not been isolated or identified. There is little evidence that the P-450 mixed-function oxidase system is followed. Van Dyke and Wineman (1971) found that the enzyme system was similar in function to a microsomal mixed-function oxidase system requiring oxygen and NADPH and small amounts of cytosol. This system slowly dechlorinated 1,2-di-^{36}Cl-ethane, but was more active with 1,1-dichloroethane, 1,1,2-trichloroethane and 1,1,2,2-tetrachloroethane. Cox et al. (1976) studied the aerobic binding to microsomal P-450 of a series of chloroalkanes. Whereas most of these compounds interacted to give a Type 1 difference spectra associated with metabolism of these substrates by direct C-hydroxylation, 1,2-dichloroethane failed to give an observable interaction.

Following 2-chloroethanol formation, Yllner (1971a, b) proposed that this alcohol was enzymatically converted to 2-chloroacetic acid via 2-chloroacetaldehyde. Chloroacetic acid was found as a major urinary metabolite of mice (Table III-2).

Johnson (1967) had observed that chloroethanol was readily dehydrogenated to chloroacetaldehyde by purified alcohol dehydrogenases from yeast or horse liver. Williams (1959) previously had suggested that chloroacetic acid appeared *in vivo* via chloroacetaldehyde. After dichloroethane administration (0.17 mg/kg), Yllner found that chloroacetic acid appeared in mouse urine in significant amounts within 24 hours where chloroethanol was only a minor metabolite (Table III-2). In addition, Kokarovtseva and Kiseleva (1978) observed that after oral administration of dichloroethane (750 mg/kg) or 2-chloroethanol (80 mg/kg) to rats, the blood level of 2-chloroethanol at 4 hours was 67.8 or 15.8 ug/ml, respectively, and declined in accordance with first-order kinetics with a half-life of about 9 hours. While chloroacetaldehyde and chloroacetic acid were not measured, these investigators suggested that a conversion of chloroethanol to chloroacetic acid occurred. The relatively low blood concentrations found after the large amounts of dichloroethane ingested and the first-order kinetics of chloroethanol metabolism were postulated to be due to initial sequestration of dichloroethane in adipose and other tissues, with a gradual diffusion redistribution as liver metabolism of dichloroethane to chloroethanol and chloroethanol to chloroacetic acid proceeded. Significant blood and liver tissue levels of chloroethanol were found even 48 hours after dosing.

The urinary metabolites found in largest amount after administration of 1,2-dichloroethane or 2-chloroacetic acid to mice (Yllner, 1971a, b) are S-carboxymethylcysteine (ca. 40 percent) and thiodiacetic acid (ca. 35 percent) (Table III-2). Yllner suggests that these metabolites arise from enzymatic conjugation (S-alkyltransferase) of chloroacetic acid with glutathione forming S-carboxymethylglutathione with chloride excision. S-carboxymethylglutathione is converted by glutathionase to S-carboxymethylcysteine, part of which is further metabolized to thiodiacetic acid (Figure III-1). Johnson (1966, 1967) has shown that S-carboxymethylglutathione is rapidly degraded by rat kidney homogenate to yield glycine, glutamic acid and S-carboxymethylcysteine. However, an alternative scheme with chloroacetaldehyde conjugation has been proposed by Johnson (1967). In his study of the metabolism of orally administered 2-chloroethanol in the rat, Johnson found that chloroethanol caused a rapid depletion of liver glutathione with a concomitant formation of S-carboxymethylglutathione. In vitro, the reaction with a rat liver cytosol fraction required stoichiometric amounts of glutathione (1 mole) and NAD (2 moles). Since pyruvate was also required for reaction, Johnson (1967) postulated that chloroethanol was converted by alcohol dehydrogenase to chloroacetaldehyde which then conjugated with glutathione to give S-formylmethylglutathione, and thence by an NAD-requiring dehydrogenation to S-carboxymethylglutathione. Johnson (1966) also has reported that chloroacetaldehyde is rapidly conjugated with glutathione in vitro by a non-enzymatic reaction at pH 7.0. Thus, Johnson concluded that this was probably the principal in vivo reaction in mammals. However, based on Yllner's results with the metabolism of chloroacetic acid (Table III-2), it appears likely that in vivo dehydrogenation of 2-chloroethanol in mammals proceeds through chloroacetaldehyde to chloroacetate before conjugation with glutathione occurs.

Recently, it also has been suggested by Rannug and Beije (1979) that there are some similarities in the biotransformation pathways of 1,2-chloroethane and vinyl chloride (Figure III-2).

Secondary Pathways

Yllner (1971a, b) observed that after dichloroethane administration to mice some 5 to 15 percent (depending on dose) was metabolized completely to CO_2 and water, and also that after chloroacetate administration small amounts of glycolic and oxalic acids appeared in urine (Tables III-1, III-2). Since these acids are known to be metabolized with CO_2, Yllner (1971 a,b) proposed that chloroacetate is enzymatically hydrolyzed to glycolate by hydrolytic dehalogenation, a portion of which is further oxidized to oxalic acid.

Yllner (1971a, b) found small amounts of S,S'-ethylene-bis-cysteine in urine of mice injected with dichloroethane (Table III-2). This metabolite was believed to occur in vivo from a reaction between dichloroethane and glutathione catalyzed by the glutathione S-alkyltransferase previously demonstrated in rat liver by Johnson (1966). The S,S'-ethylene-bis-glutathione was presumed to be further degraded to

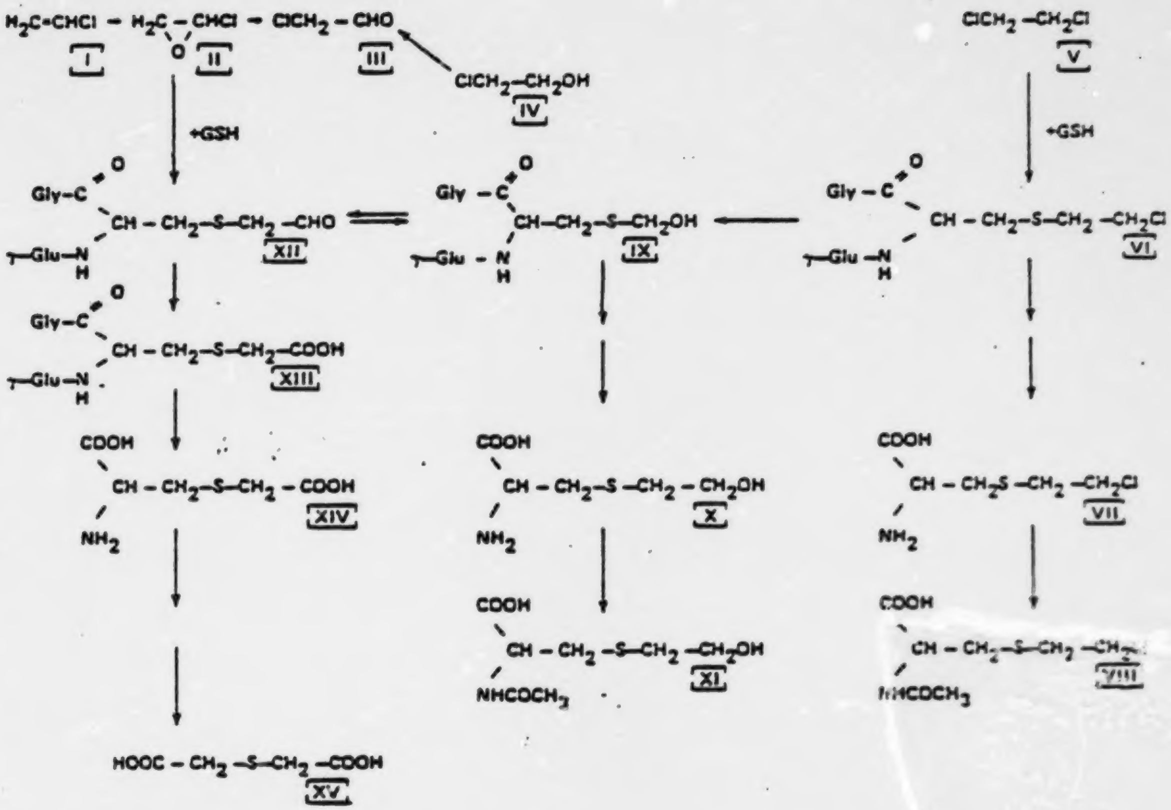

H2C=CHCl → H2C–CHCl → ClCH2–CHO
O
I
II
III
ClCH2–CH2OH
IV
ClCH2–CH2Cl
V
+GSH
+GSH
Gly–C=O
CH–CH2–S–CH2–CHO
γ-Glu–NH
XII
CH–CH2–S–CH2OH
IX
CH–CH2–S–CH2–CH2Cl
VI
CH–CH2–S–CH2–COOH
XIII
COOH
CH–CH2–S–CH2–COOH
NH2
XIV
CH–CH2–S–CH2–CH2OH
X
CH–CH2S–CH2–CH2Cl
VII
CH–CH2–S–CH2–CH2OH
NHCOCH3
XI
VIII
HOOC–CH2–S–CH2–COOH
XV

Figure ~~4~~ III-2 - Suggested metabolic main pathways of vinyl chloride (I) and DCE (V) showing similarities and differences. The illustrated pathways are in accordance with mutagenicity data and data from metabolic studies (identified urinary metabolites and depression of non-proteins sulfhydryl content *in vivo*). The following symbols have been used: I, vinyl chloride, II, chloroethylene oxide; III, chloroacetaldehyde, IV, 2-chloroethanol; V, DCE; VI, S-(2-chloroethyl) glutathione; VII, S-(2-chloroethyl) cysteine; VIII, N-acetyl-S-(2-chloroethyl) cysteine; IX, S-(2-hydroxyethyl) glutathione; X, S-(2-hydroxyethyl) cysteine; XI, N-acetyl-S-(2-hydroxyethyl) cysteine; XII, S-(2-oxoethyl) glutathione; XIII, S-(carboxymethyl) glutathione; XIV, S-(carboxymethyl) cysteine; XV, thiodiglycolic acid. (Rannug, V., and B. Beije. The Mutagenic Effect of 1,2-Dichloroethane on *Salmonella typhimurium*. II. Activation by the isolated perfused rat liver. Chem. Biol. Interaction 24:265-285, 1979).

S,S'-ethylene-bis-cysteine. Nachtomi et al. (1966, 1970) also found that an enzyme system from the soluble supernatent fraction of rat liver catalyzed a reaction between dichloroethane and glutathione to a small extent. The products were S-betahydroxyethyl-glythione and S,S'-ethylene-bis-glutathione. Earlier, Bray et al. (1952) had studied the dehalogenation of dichloroethane and other halogenated hydrocarbons by rabbit liver extracts. These workers found no evidence for enzymatic dehalogenation of dichloroethane or chloroethanol but suggested non-enzymatic dechlorination by direct interaction with sulfhydryl groups (glutathione, cysteine), a reaction which occurred with many compounds without the liver extract. Morrison and Munro (1956) showed that such a reaction occurs *in vitro* with cysteine to form S,S'-ethylene-bis-cysteine. The tendency of 1,2-dichloroethane to injure kidney tubules and cause pulmonary edema suggests that the chlorinated compound is indeed capable of reacting with sulfhydryl groups *in vivo* (Winteringham and Barnes, 1955). The quantitative studies by Yllner (1971a, b) show that this pathway involving direct reaction of dichloroethane with glutathione or cysteine could only be a minor pathway.

IV. HUMAN EXPOSURE

Humans may be exposed to 1,2-dichloroethane in drinking water, food, and air. Detailed information concerning the occurrence of and exposure to 1,2-dichloroethane in the environment is presented in another document entitled "Occurrence of 1,2-Dichloroethane in Drinking Water, Food, and Air" (Letkiewicz et al. 1983). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food, and air.

This analysis is limited to drinking water, food, and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to 1,2-dichloroethane from sources other than the three considered here, notably in occupational settings and from the use of consumer products containing 1,2-dichloroethane. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works, and travels, what one eats, and physiologic characteristics related to age, sex, and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various 1,2-dichloroethane concentrations. The 70-kg male is used for estimating intake.

a. Water

Cumulative estimates of the U.S. populations exposed to various 1,2-dichloroethane levels in drinking water from public drinking water systems are presented in Table IV-I. The values in the table were obtained using Federal Reporting Data Systems data on populations served by primary water supply systems (FRDS 1983) and the estimated number of these water systems that contain a given level of 1,2-dichloroethane. An estimated 12,232,000 individuals (5.7% of the population of 214,419,000 using public water supplies) are

Table IV-I. Total Estimated Cumulative Population (in Thousands) Exposed to 1,2-Dichloroethane in Drinking Water Exceeding the Indicated Concentration

System type	Number of people served in U.S. (thousands)	Cumulative population (thousands) exposed to concentrations (ug/l) of:			
		≥ 0.5	>5	>10	>20
Groundwater	73,473	1,235	0	0	0
Surface water	140,946	10,997	143	143	0
Total	214,419	12,232	143	143	0
(% of total)	(100%)	(5.7%)	(0.1%)	(0.1%)	(0%)

exposed to levels of 1,2-dichloroethane in drinking water at or above 0.5 ug/l, while 143,000 individuals (0.1%) are exposed to levels above 5 ug/l. It is estimated that no individuals are exposed to levels greater than 20 ug/l. Of the approximately 12 million people exposed to levels ranging from 0.5 to 5 ug/l, 11 million (90%) obtain water from surface water supplies. All exposure to 1,2-dichloroethane in drinking water at levels above 5 ug/l is expected to be from surface water sources.

No data were obtained on regional variations in the concentration of 1,2-dichloroethane in drinking water. The highest concentrations are expected to occur near sites of production and use of 1,2-dichloroethane and also, in the case of groundwater, near waste disposal sites.

Daily intake levels of 1,2-dichloroethane from drinking water were estimated using various exposure levels and the assumptions presented in Table IV-II. The data in the table suggest that the majority of the persons using public drinking water supplies would be exposed to intake levels below 0.014 ug/kg/day.

Table IV-II. Estimated Drinking Water Intake of 1,2-Dichloroethane

Exposure level (ug/l)	Persons using supplies exposed to indicated levels: Population	Persons using supplies exposed to indicated levels: % of Total Population	Intake (ug/kg/day)
≥0.5	12,232,000	5.7%	≥0.014
>5.0	143,000	0.1%	>0.14
>10	143,000	0.1%	>0.29
>20	0	0.0%	>0.57

Assumptions: 70-kg man, 2 liters of water/day.

An indication of the overall exposure of the total population to 1,2-dichloroethane can be obtained through the calculation of population-concentration values. These values are a summation of the individual levels of 1,2-dichloroethane to which each member of the population is exposed. An explanation of the derivation of these values is presented in Appendix C. Population-concentration estimates for 1,2-dichloroethane in drinking water were 7.5×10^6 ug/l x persons (best case), 3.6×10^7 ug/l x persons (mean best case), 1.4×10^8 ug/l x persons (mean worst case), and 1.6×10^8 ug/l x persons (worst case).

Assuming a consumption rate of 2 liters of water/day, population-exposure values of 1.5×10^7 ug/day x persons (best case), 7.2×10^7 ug/day x persons (mean best case), 2.8×10^8 ug/day x persons (mean worst case), and 3.2×10^8 ug/day x persons (worst case) were derived.

b. Diet

Limited data were obtained on levels of 1,2-dichloroethane in foods in the United States. These data were insufficient to use in an estimation of daily intake of 1,2-dichloroethane in the diet.

c. Air

Exposure to 1,2-dichloroethane in the atmosphere varies from one location to another. The highest level of 1,2-dichloroethane reported in the atmosphere was 240,000 ng/m^3 (240 ug/m^3) (Elfers 1979, Pellizzari 1979; cited in Brodzinsky and Singh 1982). High levels, averaging greater than 10,000 ng/m^3 (10 ug/m^3), have been detected in other areas. Normal levels, however, are somewhat lower. Brodzinsky and Singh (1982) calculated median air levels of 1,2-dichloroethane for rural/remote areas, urban/suburban areas, and source dominated areas of 0.0 ng/m^3 (0.0 ug/m^3), 490 ng/m^3 (0.49 ug/m^3), and 4,900 ng/m^3 (4.9 ug/m^3), respectively.

The monitoring data available are not sufficient to determine regional variations in exposure levels for 1,2-dichloroethane. However, urban and industrial areas appear to contain higher levels, as expected.

The daily respiratory intake of 1,2-dichloroethane from air was estimated using the assumptions presented in Table IV-III and the median and maximum levels for 1,2-dichloroethane reported above. The estimates in Table IV-III indicate that the daily 1,2-dichloroethane intake from air for adults in source dominated areas is approximately 1.6 ug/kg/day. In contrast, the intake calculated using the maximum level reported is 79 ug/kg/day; few if any persons are believed to be exposed at that level. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Table IV-III. Estimated Respiratory Intake of 1,2-Dichloroethane

Exposure (ug/m^3)	Intake (ug/kg/day)
Rural/remote (0.0)	0.0
Urban/suburban (0.49)	0.16
Source dominated (4.9)	1.6
Maximum (240)	79

Assumptions: 70-kg man, 23 m^3 of air inhaled/day (ICRP 1975).

SUMMARY

Table IV-IV presents a general view of the total amount of 1,2-dichloroethane received by an adult male from air and drinking water. Four separate exposure levels in air and five exposure levels in drinking water are shown in the tables. Insufficient data were obtained on levels of 1,2-dichloroethane in foods in the United States to assess the contribution of the diet to total 1,2-dichloroethane exposure.

The data presented have been selected from an infinite number of possible combinations of concentrations for the two sources. The actual exposures encountered would represent some finite subset of this infinite series of combinations. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to 1,2-dichloroethane at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for 1,2-dichloroethane by route of exposure. The relative dose received may vary from the relative intake. In addition, the relative effects of the chemical on the body may vary by different routes of exposure.

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of 1,2-dichloroethane of 0.49 ug/m^3 based on air monitoring data. Assuming an air level of 0.49 ug/m^3, drinking water would be the predominant source of 1,2-dichloroethane exposure in the adult male at drinking water levels above 5.6 ug/l. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of 1,2-dichloroethane in drinking water and low concentrations of 1,2-dichloroethane in ambient air and food are unknown.

Table IV-IV. Estimated Intake of 1,2-Dichloroethane from the Environment by Adult Males in ug/kg/day (% from Drinking Water)

Concentration in drinking water (ug/l)	Concentration in air			
	Rural/remote ($0.0\ ug/m^3$)	Urban/suburban ($0.49\ ug/m^3$)	Source dominated ($4.9\ ug/m^3$)	Maximum ($240\ ug/m^3$)
0	0.0 (--)	0.16 (0%)	1.6 (0%)	79 (0%)
0.5[a]	0.014 (100%)	0.17 (8.2%)	1.6 (0.9%)	79 (0.02%)
5.0[b]	0.14 (100%)	0.30 (47%)	1.7 (8.2%)	79 (0.2%)
10[c]	0.29 (100%)	0.45 (64%)	1.9 (15%)	79 (0.4%)
20[d]	0.57 (100%)	0.73 (78%)	2.2 (26%)	80 (0.7%)

Intake from each source (see Sections 5.1-5.3):

Water:
0.5 ug/l: 0.014 ug/kg/day
5.0 ug/l: 0.14 ug/kg/day
10 ug/l: 0.29 ug/kg/day
20 ug/l: 0.57 ug/kg/day

Air:
$0.0\ ug/m^3$: 0.0 ug/kg/day
$0.49\ ug/m^3$: 0.16 ug/kg/day
$4.9\ ug/m^3$: 1.6 ug/kg/day
$240\ ug/m^3$: 79 ug/kg/day

Food: Not included

[a] 12,232,000 individuals using public drinking water systems are estimated to be exposed to levels ≥ 0.5 ug/l (5.7% of population using public water supplies).

[b] 143,000 individuals using public drinking water systems are estimated to be exposed to levels > 5.0 ug/l (0.1% of population using public water supplies).

[c] 143,000 individuals using public drinking water systems are estimated to be exposed to levels > 10 ug/l (0.1% of population using public water supplies).

[d] No individuals using public drinking water systems are estimated to be exposed to levels > 20 ug/l.

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V. HEALTH EFFECTS IN ANIMALS

General

The acute and chronic toxicity of 1,2-dichloroethane exposure is not, in general, different from that observed with other halogenated aliphatic hydrocarbons. Whereas high-dose exposure to 1,2-dichloroethane causes immediate central nervous system effects leading to unconsciousness, coma, circulatory collapse and death, lower single or repeated exposures result in abnormalities of the liver, kidneys, lungs, heart, adrenals and gastrointestinal tract. These organ systems show both morphological and functional abnormalities. In part, the pathologic changes in the tissue can be ascribed to the lipophilic and electrophilic nature of the compound, but these adverse effects probably are related also to toxic metabolic products since 1,2-dichloroethane is readily and extensively metabolized. Most toxicities resulting from 1,2-dichloroethane exposure are similar for different species of animals, although there are a few manifestations which are species specific. In the animal studies which have been carried out to date, the exposure dose levels (over both acute and chronic duration) have invariably been in a range not normally encountered in the natural environment. Virtually nothing is known of the subtle toxicology of low level chronic exposures to 1,2-dichloroethane. Almost all toxicity studies reported in the literature are based on inhalation exposures; few studies have been made on toxicity resulting from ingestion, particularly via drinking water.

The narcotic properties of 1,2-dichloroethane have been known for over 100 years, but its toxicity precludes its use as an anesthetic agent. The central nervous system depression observed in a variety of species of animals is characteristic of compounds of the chloroethane series and of related halogenated aliphatic hydrocarbon compounds. In addition to central nervous system effects, other documented toxicity associated with 1,2-dichloroethane exposure in laboratory animals include damage to the liver, kidney, adrenal glands and skin, as well as pathological changes in the cardiovascular, hematological and immunological systems. A summary of these effects as well as dose data appear in the text below and in Tables V-1 through V-3. Effects on reproduction and teratogenic effects as well as mutagenicity and carcinogenicity are discussed separately below.

Acute Toxicity

The principal acute effect of 1,2-dichloroethane in mammals is central nervous system depression with unconsciousness and coma resulting from exposure to high concentrations. Visible signs of 1,2-dichloroethane poisoning include restlessness, handling intolerance, abnormal weakness, intoxication, dizziness, muscle incoordination, irregular respiration and loss of consciousness. Deaths occurring within a few hours after recovery from narcosis are usually the result of shock or cardiovascular collapse; deaths delayed by several days most often result from renal damage

TABLE V-1

Correlation of Symptoms, Exposure Time, and Concentration for Guinea Pigs Inhaling 1,2-Dichloroethane

Symptom	Average period necessary to produce symptom at various concentrations (min)				
	2000 ppm	4000-4500 ppm	10,000-17,000 ppm	25,000-35,000 ppm	60,000-70,000 ppm
Nose and eye irritation	6[a]	3-10	z 1-2	1-2	1
Unsteadiness	20-45	8-18	2-3	1-2	1-2
Inability to walk	a	30	4-10	3-5	2-4
Retching	a	b	7-15	5-13	2-4
Jerky, rapid respiration	a	b	10-30	5-13	4-8
Unconsciousness	a	30-40	10-20	4-7	3-7

[a] This symptom was not observed even after 480 min of exposure.

[b] This symptom was not observed even after 360 min of exposure.

Source: Adapted from Sayers et al., 1930.

Table ~~16~~ IV-2 Mortality after single acute exposure to 1,2-dichloroethane by inhalation

Animal	Number	Weight (g)	Time (hr)	Mortality ratio	Cumulative mortaltiy				
					0	1st day	2nd day	3rd day	4th day
				Exposure to 3000 ppm					
Mice	22		7	22/22	22				
	19		2	19/19	0	19			
Rats	20	146	7	20/20	0	19	20		
	16	177	3 1/2	15/16	0	1	3	5	13
	15	257	1 1/2	0/15					
Guinea pigs	14	885	7	14/14	0	11	13	14	
Rabbits	16	3,940	7	12/16	0	7	11	12	
Raccoons	2		7	0/2					
Cats	3	3,240	7	0/3					
Hogs	2	27,300	7	2/2	0	0	2		
				Exposures to 1500 ppm					
Mice	20		7	20/20	4	20			
	23		2	1/23	0	0	0	1	
Rats	20	170	7	4/20	0	2	2	4	
	13	257	4	0/13					
Guinea pigs	12	321	7	6/12	0	1	4	5	6

Sources: Adapted from Heppel et al., 1945, Table 1, p. 55. Reprinted by permission of the publisher.

TABLE V-3

Lethal Doses of 1,2-Dichloroethane to Nonhuman Mammals

Species	Category[a]	Dosage	Route
Mouse	LCLo	5000 mg/m^3	Inhalation
	LDLo	600 mg/kg	Oral
	LDLo	380 mg/kg	Subcutaneous
	LDLo	250 mg/kg	Intraperitoneal
Rat	LDLo	1000 ppm/4 hr	Inhalation
	LDLo	500 mg/kg	Subcutaneous
	LD_{50}	680 mg/kg	Oral
Guinea pig	LCLo	1500 ppm/7 hr	Inhalation
	LDLo	600 mg/kg	Intraperitoneal
Rabbit	LCLo	3000 ppm/7 hr	Inhalation
	LDLo	1200 mg/kg	Subcutaneous
	LD_{50}	860 mg/kg	Oral
Dog	LDLo	2000 mg/kg	Oral
	LDLo	175 mg/kg	Intravenous
Pig	LCLo	3000 ppm/7 hr	Inhalation

[a] LCLo - lowest published lethal concentration in air;
LDLo - lowest reported lethal dose by any route other than inhalation; LD_{50} - median lethal dose by any route other than inhalation.

Source: Adapted from NIOSH, 1977, p. 388.

(Spencer et al., 1951; Irish, 1963). Despite these qualitative statements, the manner in which 1,2-dichloroethane exerts its lethal effects in mammals cannot always be easily identified or characterized. For example, Heppel et al. (1946) stated, "In spite of the fact that this important compound has been extensively studied in this laboratory for nearly three years, it must be admitted that the exact mechanism of death remains obscure." Since that time, it has become generally accepted that 1,2-DCE causes death by direct effects on the central nervous system (CNS).

Weakness, disordered, vertiginous movement, persistent thirst, eye and nasal irritation, static and motor ataxia, retching movements and marked changes in respiration are common signs of acute 1,2-dichloroethane poisoning in non-human animals. Sayers et al. (1930) observed all of these signs in guinea pigs after less than 10 minutes' exposure to 60,000 ppm 1,2-dichloroethane and in 25 minutes to 10,000 ppm (Table V-1). However, no signs of poisoning were apparent following exposure at 1200 ppm for 8 hours. Death occurred in less than 30 minutes with animals exposed to 60,000 ppm and usually after about a day following a 25-minute exposure to 10,000 ppm. Congestion and edema of the lungs and generalized passive congestion throughout the visceral organs were commonly observed in animals that died during exposure. Renal hyperemia and pulmonary congestion and edema were typical conditions in animals that died one to eight days following exposure. Similar histopathological lesions, as well as fatty degeneration of the myocardium and renal tubular epithelium, also were reported by other observers who exposed mice, rats, guinea pigs, rabbits, cats and dogs sufficiently long to air containing 1000 to 3000 ppm 1,2-dichloroethane (Heppel et al., 1945, 1946; Spencer, et al., 1951).

The acute toxicity of 1,2-dichloroethane varies with species and route of exposure. In general, it appears to be more toxic to mammals than is carbon tetrachloride (Hofmann, et al., 1971). Table V-2 summarizes mortality in seven species of animals due to a single acute exposure by inhalation that varied in duration from 1.5 to 7 hours. Few animals survived exposure at 3000 or 1500 ppm for 7 hours, but death was frequently delayed for days in some species. Congestion of the viscera and degeneration of the liver and kidneys were common findings among these animals (Heppel et al., 1945).

Data published by the National Institute for Occupational Safety and Health (NIOSH, 1978) indicate that, for exposure by inhalation, the lowest doses that are lethal for a variety of common mammalian species range from about 1000 ppm for 4 hours to about 3000 ppm for 7 hours. In contrast, a dose of 175 mg/kg administered intravenously is lethal in the dog (NIOSH, 1977). Other minimum lethal doses are indicated in Table V-3.

The effects of acute exposure to 1,2-dichloroethane are also strongly dependent on the concentration of the toxicant. For example, when rats were exposed to air containing 1000 ppm 1,2-dichloroethane, 7.20 hours elapsed before half the population died; however, with concentrations of 3000 and 12,000 ppm, the median lethal response times decreased to 2.75 and 0.53 hours, respectively (Spencer et al., 1951). Similarly, when male guinea pigs were injected intraperitoneally with 150 or 300 mg/kg 1,2-dichloroethane in corn oil, no noticeable hepatotoxic effects occurred; when 600 mg/kg was injected, a low order of damage occurred, as measured by increased serum concentrations of ornithine carbamyl transferase (DiVincenzo and Krasavage, 1974). 1,2-Dichloroethane also exhibits concentration-dependent nephrotoxic characteristics when it is injected intraperitoneally into male Swiss mice. Plaa and Larson (1965) observed a progressive increase in the number of mice (10%, 30% and 56%) having excessive urinary protein, but not excessive urinary glucose, following injection of 0.075, 0.2 and 0.4 ml of 1,2-dichloroethane per kilogram of body weight. It should be noted, however, that the last cited dose is well above the minimum lethal dose for mice.

Duprat, et al. (1976) studied the irritant property of 1,2-dichloroethane and other simple chlorinated hydrocarbons by making a single application or installation of the solvents to the skin or eye of rabbits and then following the course of the resulting lesions macroscopically and histologically.

1,2-Dichloroethane was rated a primary irritant in both applications but was considered less potent as a skin irritant than perchloroethylene, chloroform, 1,1,2-trichloroethane, trichloroethylene and methylene chloride. As an eye irritant, 1,2-dichloroethane was classified less potent than chloroform, methylene chloride, dichloroethylene, trichloroethylene and trichloroethane.

Although acute exposures to 1,2-dichloroethane produce roughly similar responses in many mammalian species, the systemic administration of this compound to dogs produces one effect not ordinarily seen in other mammalian species: clouding of the cornea. Typically, there is a necrosis of the endothelium beginning in the basal portions of the cells, followed by secondary swelling of the stroma, formation of excess basement membrane and thickening of Descemet's layer. This response also occurs in cats and rabbits when 1,2-dichloroethane is injected directly into the anterior chamber of the eye but not with systemic administration of the compound. The unique response of the dog eye appears to result from a greater amount of 1,2-dichloroethane coming in contact with the dog endothelium rather than from any unusual susceptibility of the eye itself (Heppel et al., 1944; Kuwabara, et al., 1968).

Longer Term Exposures

Longer-term exposures of rats and guinea pigs to air containing 100 ppm 1,2-dichloroethane for 7 hours per day, five days per week for several months generally produced no deaths and no evidence of adverse effects as judged by general appearance, behavior, mortality, growth, organ function or blood chemical chemistry (Heppel, et al., 1946; Spencer, et al., 1951; Hofmann, et al., 1971). However, similar exposures of rats, guinea pigs, rabbits and monkeys to air containing 400 or 500 ppm 1,2-dichloroethane usually resulted in high mortality and a limited number of varying pathological findings, including pulmonary congestion, diffuse myocarditis, slight to moderate fatty degeneration of the liver, kidney, adrenal and heart, and prolonged plasma prothrombin time (Heppel, et al., 1946; Spencer, et al., 1951; Hofmann, et al., 1971). Different effects were observed in rabbits exposed to high concentrations of 1,2-dichloroethane for a few hours/day over extended periods of time. After inhaling 3000 ppm 1,2-dichloroethane for 2 hours per day, five days per week for 90 days, rabbits exhibited varying degrees of anemia accompanied by leukopenia and thromobocytopenia. In addition, there was frequent hypoplasia of the granuloblastic and erythroblastic parenchyma in the bone marrow. The cellular concentration of leukolipids was reduced, but no change occurred in polysaccharides, peroxidase, or ribonucleic acid. In view of these findings, the authors suggested that 1,2-dichloroethane might exert a direct poisoning effect on bone marrow (Lioia and Elmino, 1959; Lioia, et al., 1959).

Reproduction and Teratology

In a series of studies, Vozovaya (1971, 1974, 1975, 1976) exposed female white rats (strain not stated) to air containing 57 mg/m^3 (14 ppm) 1,2-dichloroethane for 4 hours per day, six days per week for six to nine months to determine the effects of this compound on reproductive function of these animals and on the development of progeny. Fertility of the treated rats decreased and the number of still births increased relative to controls. Viability of first generation offspring decreased. First generation females exhibited prolonged estrus and a high perinatal mortality rate. These effects were augumented and others were observed when rats were exposed in similar experiments to mixtures of 1,2-dichloroethane (30 ± 10 mg/m^3) and gasoline (1210 ± 70 mg/m^3). In particular, a decrease in the incidence of conception occurred which was not seen during similar exposures to the separate compounds. In addition, there was a significant decrease in the viability of first generation offspring. For example, at the end of the sixth month, mortality in the group exposed to 1,2-dichloroethane alone was 25.0 ± 6.92% as compared with 5.4 ± 3.75% in the controls ($P < 0.05$). However, for the group exposed to the combination of 1,2-dichloroethane and gasoline, mortality ($P < 0.05$) was 28.0 ± 9.16% (Vozovaya, 1975). In a later study in which 108 random-bred female white rats were exposed to gasoline (31.0 ± 33 mg/m^3) and 1,2-dichloroethane (15 ± 3 mg/m^3) separately and in combination 4 hours per day, six days per week for four months, Vozovaya (1976) found increased numbers of degenerative follicles in the ovaries of rats exposed to the mixture of compounds but not in ovaries of rats exposed to the compounds separately. In the affected rats, a high total embryonic mortality was caused by a high rate of preimplantation deaths and also by a high rate of resorptions of embryos at an early stage of development.

In other studies, Alumot and co-workers (1976) added 250 or 500 ppm 1,2-dichloroethane, with appropriate precaution to avoid losses by volatilization, to the food of rats for two years. No significant differences were found between these animals and controls with respect to growth, feed consumption or feed efficiency. At the levels tested, the added 1,2-dichloroethane had no effect on male fertility or reproductive activity of rats of either sex. Based on the results of this study, the authors recommended an acceptable daily intake and tolerance of 1,2-dichloroethane in human food of 0.07 mg/kg of body weight and 10 ppm, respectively.

Inhaled 1,2-dichloroethane is transported into the uterus and ovaries of non-pregnant rats. During pregnancy it passes through the placental barrier of rats and is accumulated in fetal tissues, especially the liver (Vozovaya and Malyarova, 1975).

Rao, et al. (1980) studied the effect of inhaled 1,2-dichloroethane on embryonal and fetal development in rats and rabbits and on the reproductive capacity of rats. For the teratology studies, 16-30 pregnant Sprague-Dawley rats were exposed to 0, 100 or 300 ppm 7 hours/day on Days 6-15 of gestation. Rabbits (19-21 per group) were exposed to the same concentrations of dichloroethane on Days 6-18 of pregnancy. Rats were sacrificed on Day 21, rabbits on Day 29 of gestation.

Ten of the 16 rats exposed to 300 ppm died. Animals in this high dose group exhibited lethargy, ataxia, decreased body weight and food consumption and vaginal bleeding prior to death. No deaths occurred in the low dose group or the controls. Only one rat in the high dose group exhibited implantation sites; all implantations were resorbed. Exposure to 100 ppm did not effect mean litter size, numbers of resorptions or fetal body measurements. The number of litters/group was decreased (15/30 as compared with 22/30 in the control group). No teratological changes were observed at any dose.

Three of 19 rabbits in the high dose group died, as did 4 of 21 in the low dose group. The incidence of pregnancy was not affected, as it had been in the rat. There was no effect on mean litter size, incidence of resorptions, fetal body measurements or maternal body weights. In addition, no alteration in the incidence of major malformations was observed at either dose.

In the reproductive study, 20 Sprague-Dawley rats/sex/group were exposed at levels of 0, 25, 75 or 150 ppm 1,2-dichloroethane. During 60-day prebreeding period, the animals were exposed for 6 hours/day, 5 days/week. During the breeding period and gestation, they were exposed 6 hours/day, 7 days/week. Females who delivered litters were not exposed from Day 21 of gestation through the fourth day post-parturition so as to allow for delivery and rearing of the offspring.

No significant changes in body weight occurred during the prebreeding periods. Female body weights during gestation and rearing of both F/1a and F/1b litters were unaffected. Food consumption by males in the 150 ppm dose group increased significantly in the latter part of the study. In the females, a decrease in food consumption occurred in the high and middle dose groups during the first week, but returned to normal afterwards. Of all the indices measured, only the average number of pups per litter (both live and dead) at birth was significantly lower in the 75 ppm group. Kidney weights of F/1b male in the 75 ppm group were significantly higher when measured at sacrifice on Day 21 of age. No histological changes accompanied this change.

The only teratology/reproductive function study to date which the test animals were exposed to 1,2-dichloroethane in their drinking water was reported by Lane, et al, (1982). The authors conducted a modified multigeneration reproduction study which included screening for dominant lethal and teratogenic effects. Male and female ICR Swiss mice received 1,2-dichloroethane at concentrations of 0, 0.03, 0.09 or 0.29 mg/l in drinking solution (1% Emulphor in deionized water, v/v). These concentrations were designed to correspond to daily doses of 0,5,15 or 50 mg/kg bw. Two control groups were used: 1) untreated, and 2) 1% Emulphor vehicle.

The F/O mice were randomized into test groups of 10 males and 30 females, acclimated for 2 weeks and then placed upon the appropriate testing regimen. After 35 days on the test regimen, the now 14-week olds were randomly mated to produce the F/1A litters. Two weeks after weaning of the F/1A litters, the F/O adults were rerandomized and remated to produce the F/1B litters. Parental stock for the second generation was drawn from these F/1B offspring. F/O females were rested for 2 weeks following weaning of the F/1B pups. The offspring from the F/1C mating were used in the dominant lethal and teratology screening. By the end of the experiment, the F/O adults had been exposed to 1,2-DCE in their drinking water for a total of 25 weeks.

At weaning, the F/1B litters were culled to 30 females and 10 males/group. Matings between siblings were avoided. The F/1B weanings were placed on the testing regimen and when reaching 14 weeks of age, were randomly mated to produce the F/2A litters. Two weeks after these offspring were weaned, the F/1B adults were remated randomly to produce the F/2B offspring which were used in the dominant lethal and teratology screening. By the end of the experiment, the F/1B adults had been exposed to the drinking water solutions for a total of 24 weeks.

Weekly body weight and twice-weekly fluid consumption data were collected for the F/O and F/1B adult mice throughout the study. The authors stated that there were no statistically significant differences seen in either of these parameters.

However, no data were presented in the paper so the reader could not make a judgment about the validity of that conclusion. Mortality rates in the same two adult groups also were monitored. These are summarized in Table V-4. Significant numbers of the animals in the low dose group of F/O adults died (20% of the males, 13.3% of the females compared with no male controls and only 3.3% of the female controls). However, this death rate appeared not to be dose-related, as it did not increase at the higher two doses. Among the F/1B adults, more controls died than did treated animals.

TABLE V-4

Percentage Mortality Among Males and Females
Ingesting 1,2-Dichloroethane
Mofified from Lane et. al, 1982

Compound	Concentration (mg/ml)	F/10 percentage Mortality[a]		F/1B percentage Mortality[b]	
		Males	Females	Males	Females
1,2-Dichloroethane (1,2-DCE)	0.00[c]	0.0	3.3	20.0	7.4
	0.00[d]	0.0	3.3	0.0	0.0
	0.03	20.0	13.3	0.0	3.3
	0.09	0.0	6.7	0.0	3.3
	0.29	0.0	0.0	0.0	0.0

[A] After 25 weeks of dosing.
[b] After 24 weeks of dosing.
[c] Naive control.
[d] 1% Emulphor vehicle control.

Adult reproductive performance was monitored in the F/O and F/1B adults, as they produced the F/1A and F/1B generations (F/O) and the F/2A generation (F/1B). The fertility and gestation indices (F1 and G1, respectively) are shown in Table V-5. No significant dose-related differences were seen in any treatment group when compared with the controls.

TABLE V-5

Reproductive Performance of Adult Mice Ingesting 1,2-Dichloroethane (Modified from Lane, et al, 1982)

Concentration	Litter					
	F/1A		F/1B		F/2A	
(mg/ml)	FI[a]	GI[b]	FI	GI	FI	GI
0.00[c]	90.0	92.6	70.0	71.4	76.2	100.0
0.00[d]	93.3	82.1	76.7	78.2	86.2	96.0
0.03	89.3	92.0	89.3	84.0	93.1	81.5
0.09	82.8	83.3	62.1	94.4	82.8	100.0
0.29	90.0	85.2	70.0	90.5	85.2	78.3

---

[a] FI (Fertility Index) = (No. females pregnant/no. females mated) X 100.

[b] GI (Gestation Index) = (No. females with live litters/no. females pregnant) X 100.

[c] Naive control.

[d] Emulphor vehicle control.

Twenty-one day litter survival studies were conducted on litters of the F/1A, F/1B and F/2A generations. Litter size was recorded on Days 0, 4, 7, 14 and 21. Offspring were weighed collectively on Days 7 and 14 and individually on Day 21. Viability and lactation indices (VI and LI, respectively) also were calculated. 1,2-Dichloroethane, at the doses administered, did not cause any significant adverse intergenerational or transgenerational effects on mean litter size at birth (Table V-6), mean postnatal body weights (Table V-7) and survival indices (Table V-8). Values of the F/2A postnatal body weights (Table V-7) and survival indices (Table V-8) were decreased from the F/1A and F/1B values with few exceptions. The decrease occurred in all groups, including both controls, and thus was believed not to be treatment-related. Necropsies of weanlings from these groups yielded no evidence of dose-dependent gross pathology or congenital malformation.

Findings from the dominant lethal screening are presented in Table V-9. Statistically significant effects in the ratio of dead to live fetuses (DF/LF) were observed in both generations. However, these effects did not appear to be dose-related, since there were both increases and decreases as observed when compared with the controls. The frequency (F%) of dominant lethal factors in both generations was minimal (-7 to +8).

TABLE V-6

Mean Litter Size At Birth[a] of Mice Ingesting 1,2-Dichloroethane (Modified from Lane, et al., 1982)

Compound	Concentration (mg/ml)	Litter		
		F/1A	F/1B	F/2A
1,2-Dichloroethane (1,2-DCE)	0.00[b]	13.1 ± 3.2	13.1 ± 4.5	11.8 ± 2.4
	0.00[c]	12.0 ± 2.3	12.1 ± 3.0	12.2 ± 2.1
	0.03	13.2 ± 3.2	12.5 ± 4.1	11.3 ± 3.8
	0.09	12.9 ± 2.7	10.5 ± 4.4	12.3 ± 2.7
	0.29	11.4 ± 2.7	10.4 ± 4.8	12.6 ± 1.9

[a] Mean pups per litter ± SD.
[b] Naive control.
[c] 1% Emulphor vehicle control

TABLE V-7

Mean Postnatal Body Weights[a] of Offspring Of
Mice Ingesting 1,2-Dichloroethane
(Modified from Lane, et al, 1982)

	Litter								
	F/1A			F/1B			F/2A		
	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21
1,2-DCE concentration (mg/ml)									
0.00[b]	4.8 ± 1.0	7.1 ± 1.3	11.0 ± 2.4	4.8 ± 0.8	7.7 ± 1.5	12.0 ± 1.5	3.7 ± 1.2	5.2 ± 2.2	7.1 ± 3.3
0.00[c]	4.8 ± 0.5	7.5 ± 0.7	11.5 ± 1.5	5.0 ± 0.5	8.0 ± 0.7	12.7 ± 4.1	4.0 ± 0.6	5.7 ± 1.5	7.6 ± 2.9
0.03	4.8 ± 0.5	7.1 ± 0.8	10.5 ± 1.8	5.0 ± 0.4	7.9 ± 0.7	12.2 ± 1.3	4.7 ± 0.9	7.0 ± 1.6	9.7 ± 2.9
0.09	4.7 ± 0.7	7.4 ± 1.1	10.9 ± 1.8	5.0 ± 0.8	7.6 ± 1.0	11.0 ± 2.2	3.7 ± 1.1	5.3 ± 2.0	7.1 ± 2.7
0.29	5.1 ± 0.6	7.1 ± 0.9	10.7 ± 1.7	4.9 ± 0.7	7.8 ± 1.4	11.0 ± 2.3	4.4 ± 0.5	6.6 ± 0.9	8.9 ± 1.1

[a] Mean pup body weight (g) ± SD.
[b] Naive control.
[c] 1% Emulphor vehicle control.

TABLE V-8

Survival Indices for Litters of Mice Ingesting 1,2-Dichloroethane[a] (Modified from Lane, et al, 1982)

Concentration (mg/ml)	Litter					
	F/1A		F/1B		F/2A	
	VI[b]	LI[c]	VI	LI	VI	LI
0.00[d]	97.2	94.8	96.9	90.4	88.5	86.3
0.00[c]	97.5	98.2	94.0	94.4	89.6	81.3
0.03	98.1	97.8	96.7	96.4	91.8	95.0
0.09	94.3	97.5	97.0	99.0	89.6	86.8
0.29	93.0	97.2	93.1	97.7	92.3	89.6

[a] The F/1C and F/2B pregnancies were interrupted for dominant lethal and teratology studies.

[b] VI (viability index) = $\frac{\text{(Day 4 litter size)i}}{\text{(Day 0 litter size)i}}$ N = No. litters

[c] LI (lactation index) = $\frac{\text{(Day 21 litter size)i}}{\text{(pups kept at Day 4)i}}$ N = No.litters. Pu
kept at Day 4 =

[d] Naive control.
[e] 1% Emulphor vehicle control.

TABLE V-9

Results of Dominant Lethal Screening in Females Mated to Males Ingesting 1,2-Dichloroethane (Modifified from Lane, et al., 1982)

	Concentration (mg/ml)	Number pregnant	Fertility Index[a]	Implants[b]	Resorptions[b]	Live fetuses[b]	DF/LF	DF > 1	DF > 2	FL%
F/1C	0.00[c]	17	56.7	14.1	1.4	12.7	23/216	9/8	6/11	
Mating	0.00[d]	19	63.3	14.0	0.7	13.3	13/252*	11/8	2/17	-1.89
	0.03	16	66.6	14.0	1.6	12.4	26/198*	8/8	1/15	2.60
	0.09	23	76.7	14.5	0.9	13.6	21/312	16/7	5/18	-6.77
	0.29	17	56.7	13.2	0.6	12.5	11/213	7/10	2/15	1.42
F/2B	0.00[c]	15	62.5	12.2	1.0	11.2	15/168	3/12	1/14	
Mating	0.00[d]	25	83.3	11.6	0.8	10.8	19/271	9/16	3/22	3.21
	0.03	27	90.0	12.3	0.9	11.4	23/309	14/13	5/22	-2.14
	0.09	24	80.0	12.0	1.7	10.3	40/247*	12/12	5/19	8.13
	0.29	16	63.3	10.9	0.1	10.8	2/172*	2/14	0/16	4.02

[a] Indices defined:

$$\text{Fertility index} = \frac{\text{number of females pregnant}}{\text{number of females available}} \times 100$$

$$\text{DF/LF} = \frac{\text{total number of dead fetuses}}{\text{total number of live fetuses}}$$

$$\text{DF} \geq 1 = \frac{\text{total number of females with one or more dead fetuses}}{\text{total number of females with zero dead fetuses}}$$

- continued next page -

$$\text{DF} \geq 2 = \frac{\text{total number of females with two or more dead fetuses}}{\text{total number of females with less than two dead fetuses}}$$

$$\text{FL\% (frequency of dominant lethal factors)} = \left[1 - \frac{\text{mean live fetuses, treatment}}{\text{mean live fetuses, naive}}\right] \text{X } 100 \text{ (Ehling et al., 1978)}$$

[b] Mean value per dam.
[c] Naive control.
[d] 1% Emulphor vehicle control.

* Significantly different from control at $p \leq 0.05$.
Vehicle controls were compared to naive controls;
treatment groups were compared with their vehicle controls.

Maternal ingestion of 1,2-dichloroethane did not produce any apparent adverse reproductive effects (Table V-10) or increased incidences of fetal visceral or skeletal abnormalities (Table V-11). The authors concluded, therefore, that, at the doses tested, 1,2-dichloroethane did not present a hazard to reproduction and development.

CARCINOGENICITY

Because of its structure, 1,2-dichcloroethane has been classified as a substance having limited suspicion of carcinogenicity (U.S. EPA, 1977c); nonetheless, several studies have addressed the carcinogenic potential of this compound.

In an inhalation study lasting 212 days, Spencer et al. (1951) found no evidence of carcinogenic activity when Wistar rats were exposed 151 times to 200 ppm 1,2-dichloroethane for 7 hours per day. More recently, in an inhalation study at the Montedison Research Institute in Bologna, Maltoni (as cited in Albert, 1978) separately exposed 90 male and 90 female Swiss mice and Sprague-Dawley rats 7 hours daily, five times weekly, to 0, 5, 10, 50, or 150 ppm 1,2-dichloroethane. Initially, the highest exposure was 250 ppm, but this was reduced after ten weeks to 150 ppm because the animals could not tolerate the higher concentration. After exposure of 1 1/2 years' duration, surviving animals were to be held until the end of their natural lives. In an interim report after 78 weeks of exposure and 26 weeks of observation, Maltoni

TABLE V-10

Results of Teratology Screening in Females Ingesting 1,2-Dichloroethane

(Modified from Lane, et al., 1982)

	Concentration (mg/ml)	No. of liters	Fecundity Index[a]	Implants[b]	Resorptions[b]	Live fetuses[b]	DF/LF [a]	DF 1[a]	DF 2[a]	M:F[a]
F1/C mating	0.00[c]	9	90.0	12.0	1.8	10.2	16/92	4/5	1/8	49:51
	0.00[d]	8	100.0	12.1	5.6	6.5	47/51*	6/2	6/2*	59:41
	0.03	10	100.0	14.9	2.5	12.4	25/121*	6/4	5/5	48:52
	0.09	6	100.0	13.8	5.3	8.5	32/51	5/1	3/3	48:52
	0.29	8	80.0	13.4	1.0	12.4	8/99*	3/5	2/6	43:57
F/2B mating	0.00[c]	9	100.0	14.1	1.0	13.1	9/118	7/2	2/7	47:53
	0.00[d]	6	100.0	14.5	2.7	11.8	17/71*	3/3	2/4	39:61
	0.03	4	100.0	16.0	0.8	15.2	3/61*	2/2	1/3	57:43
	0.09	9	100.0	13.1	2.7	10.5	24/94	5/4	2/7	46:54
	0.29	6	85.7	13.0	0.7	12.3	5/74*	5/1	0/6	49:51

[A] Indices defined: Fecundity index = percentage of copulation plug-positive females bearing live fetus(es) at sacrifice. DF/LF= ratio of dead fetuses to live fetuses. M:F = ratio of live male to female fetuses expressed as a percentage of the total number of live fetuses.

[b] Mean value per dam.

[c] 1% Naive control.

[d] 1% Emulphor vehicle control.

*Significantly different from control at $p \leq 0.05$. Vehicle controls were compared to naive controls; treatment groups were compared with their vehicle controls.

TABLE V-11

Distribution of Visceral and Skeletal Malformations Among Fetuses/Litters of Females Ingesting 1,2-DCE

(Modified from Lane, et al., 1982)

	F/1C litters					F/2B litters				
Conc. (mg/ml):	0.00[a]	0.000[b]	0.03	0.09	0.29	0.00[a]	0.00[b]	0.03	0.09	0.29
Total No. fetuses/total No. litters:	92/9	51/8	121/10	51/6	99/8	118/9	71/6	61/9	94/9	74/6
Visceral malformations										
Total number examined	33/8	19/7	46/9	18/4	29/7	38/9	24/5	20/4	29/8	24/6
Hydrocephalus	0/0	0/0	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Cleft palate	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Atrial, ventricular, or cardiac hypertrophy	0/0	0/0	1/1	0/0	0/0	0/0	1/1	0/0	1/1	0/0
Malrotation of the heart	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Hydronephrosis	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Dilated renal pelvis	0/0	1/1	0/0	2/1	1/1	1/1	0/0	0/0	0/0	0/0
Dilated bladder	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Cryptorchidism/malpositioned testis	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Skeletal malformations										
Total number examined			(c)			80/9	47/5	41/4	65/8	50/6
Dyplastic skull						0/0	0/0	0/0	0/0	1/1
Dysplastic supraoccipital region						3/2	3/2	0/0	2/2	1/1
Microagnathia						0/0	0/0	0/0	0/0	0/0
Asymetric stenebrae						24/6	9/4	2/2	9/5	16/6
Bifid sternebrae						8/3	1/1	7/2	4/3	5/3
Hypoplastic sternebrae						3/1	0/0	0/0	0/0	1/1
Extra ribs						2/2	1/1	0/0	2/2	2/2
Wavy ribs						0/0	0/0	0/0	1/1	0/0

[a] Navie control.

[b] 1% Emul[illegible] vehicle control.

indicated that he "has found no evidence of any exceptional tumors in rats or mice" (Albert, 1978). This conclusion was qualified as "almost conclusive." The animals were allowed to live until spontaneous death.

After more than 60,000 pathologic slides were examined, the authors concluded the 1,2-DCE did not show carcinogenic effects under the experimental conditions (Maltoni, et al., 1980). The negative results may be explained by the fact that Maltoni, et al. did not follow NCI guidelines in the conduct of their study. On the other hand, Maltoni, et al., (1980) noted several factors which could be involved: the route of administration of 1,2-DCE; the purity of the compound used; the possibility of laboratory pollution; the size of both treated and control animal groups; the professionality of the study team, the different strains of animals used; and the possible differences in pathological interpretation.

In 1977, Theiss et al. reported on an investigation of the carcinogenic potential of 1,2-dichloroethane and other organic contaminants of U.S. drinking water by injecting the compounds intraperitoneally into six- to eight-week-old strain A/St male. Each dose of reagent grade 1,2-dichloroethane was injected into groups of 20 mice three times a week for 24 injections. Three dose levels were used: 20, 40, and 100 mg/kg in each injection; 100 mg/kg was the maximum tolerated dose. Tricaprylin was used as the vehicle. Twenty-four weeks after the first injection, the mice were sacrified and their lungs were placed in Tellyesniczky's fluid. After 48 hours the lungs were examined microscopically for surface adenomas. The frequency of lung tumors in each group was compared with that in a vehicle-treated control group by means of the Student's "t" test. The incidence of lung tumor increased with dose, but none of the groups had pulmonary adenoma responses that that were significantly greater ($P < 0.05$) than that of the vehicle-treated control mice.

NCI Bioassay

Two studies of the carcinogenicity of 1,2-dichloroethane were performed for the National Cancer Institute (NCI) by the Hazleton Laboratories, Inc., Vienna, Virginia. The results of both were released by NCI on September 26, 1978. In one of these studies, 200 8-week-old Osborne-Mendel rats were exposed to technical grade 1,2-dichloroethane delivered by oral intubation. Fifty rats of each sex separately received either the maximum tolerated dose (95 mg/kg daily, time-weighted average dosage over a 78-week period) or one-half of this dose. Twenty rats of each sex served as untreated controls, and an equal number were given the vehicle (corn oil) by intubation. Survival of male rats exposed to the high dose was low: 50% (25/50) were alive by week 55, but only 16% (8/50) lived to week 75. None survived the study. Male rats in other groups fared better: in the low dose group, 52% (26/50) survived at least 82 weeks, and, in the untreated control group, 50% (10/50) survived at least 87 weeks. The survival rate of female rats exposed to the high dose was 50% (25/50) by week 57 and 20% (10/50) by week 75. Half (25/50) of the female rats in the low-dose group survived at least 85 weeks. Terminal survival times for all groups are shown in Table V-12.

Gross necropsies were performed on animals dying during the experiment or killed at the end. Twenty-eight organs, as well as all tissues containing visible lesions, were fixed in 10% buffered formalin, embedded in paraplast and sectioned for microscopic examination. Diagnoses of any tumors and other lesions were coded according to the Systematized Nomenclature of Pathology of the College of American Pathologists, 1965. Squamous-cell carcinomas of the fore-stomach occurred in 18% of the high-dose males and in 6% of the low-dose males but were not found in the controls. The Cochran-Armitage test included a significant positive association between dosage and the incidence of squamous-cell carcinomas in these animals. The Fisher exact test also confirmed the significance of these results (P = 0.001) when comparison was made between the high-dose group and the pooled vehicle control group. Only one squamous-cell carcinoma of the fore-stomach occurred in the exposed female rats and none were found in the controls (Table V-13).

TABLE V-12

Terminal Survival of Rats in Experimental and Control Groups Involved in Carcinogenicity Studies with 1,2-Dichloroethane

	MALES		FEMALES	
Group	Weeks in study	Animals alive at end of study	Weeks in study	Animals alive at end of study
Untreated controls[a]	106	4/20 (20%)	106	13/20 (65%)
Vehicle controls	110	4/20 (20%)	110	8/20 (40%)
Low-dose group	110	1/50 (2%)	101	1/50 (2%)
High-dose group[b]	101	0/50 (0%)	93	0/50 (0%)

[a] Five male and female rats were sacrificed at 75 weeks of study.

[b] All animals in this group died before the bioassay was terminated.

Source: Adapted from Albert, 1978, Table I, p. 15.

TABLE V-13

Squamous-cell Carcinomas of the Forestomach in 1,2-Dichloroethane-treated Rats

Group	Rats with squamous-cell carcinoma of forestomach
Males	
Untreated controls	0/20 (0%)
Vehicle controls	0/20 (0%)
Low-dose group	3/50 (6%)
High-dose group	9/50[a] (18%)
Females	
Untreated controls	0/20 (0%)
Vehicle controls	0/20 (0%)
Low-dose group	1/49 (2%)
High-dose group	0/50 (0%)

[a] A squamous-cell carcinoma of forestomach metastasized in one male of high-dose group.

Source: Adapted from National Cancer Institute, 1978.

Hemagiosarcomas also occurred in exposed male and female rats but not in the control animals (Table V-14). They were seen in the spleen, liver, adrenals, pancreas, large intestine and abdominal cavity. Low-dose animals had higher incidences of hemangiosarcoma than high-dose animals. The Cochran-Armitage test indicated a significant (P = 0.021) positive association between dosage and the incidence of circulatory system hemangiosarcoma in males, but not females, when dosed groups were compared with the pooled vehicle control group. The Fisher exact test confirmed these findings with statistically significant probability values as follows: P = 0.016 for high-dose males versus pooled control and P = 0.003 for low-dose males versus pooled control.

The NCI rat study also showed significant increases in the incidence of mammary adenocarcinomas in treated female rats. In the high-dose group, tumors were noticed as early as 20 weeks after treatment. Eventually 36% (18/50) of this group developed lesions (Table V-15). The Cochran-Armitage test indicated significant (P = 0.001) positive association between the dosage and the incidence of mammary carcinomas when results were compared with either control group. The Fisher exact tests were significant when compared with the high-dose group and either the matched vehicle group (P = 0.001) or the pooled vehicle control group (P = 0.002). Historically, adenocarcinomas of the mammary gland occur in 2% (4/200) of the vehicle control females.

TABLE V-14

Hemangiosarcomas in 1,2-Dichloroethane-treated Rats[a]

Males		Females	
Low-dose	High-dose[b]	Low-dose[c]	High-dose
11/50 (22%)	5/50 (10%)	5/50 (10%)	4/50 (8%)

[a] No hemangiosarcomas were found in male or female controls.

[b] Only 49 animals were examined for hemangiosarcomas of the spleen and adrenals and 48 for hemangiosarcomas of the pancreas.

[c] Only 48 animals were examined for hemangiosarcomas of the large intestine.

Source: Adapted from National Cancer Institute, 1978.

TABLE V-15

Adenocarcinomas of the Mammary Gland in 1,2-Dichloroethane-treated Female Rats

Untreated controls	Vehicle controls	1,2-Dichloroethane-treated rats	
		Low-dose	High-dose
2/20 (10%)	0/20 (0%)	1/50 (2%)	18/50 (36%)

Source: Adapted from NCI, 1978.

In summary, the NCI study indicates a positive association between exposure to 1,2-dichloroethane and the incidence in male, but not female, rats of squamous-cell carcinomas of the forestomach and hemangiosarcomas of the circulatory system. The study also statistically links an incrased incidence of adenocarcinomas of the mammary gland in female rats with exposure to technical grade 1,2-dichloroethane. Analysis of purity performed by NIOSH after completion of the bioassay showed that there was about 99% 1,2-DCE, along with chloroform as the major contaminant as well as 12 other minor contaminants (Hooper, et al., 1980).

The second NCI carcinogenic study of 1,2-dichloroethane used 200 5-week-old B6C3F1 mice instead of rats. Fifty male and female mice were administered technical grade 1,2-dichloroethane in maximum tolerated doses or in half of the maximum tolerated dose by oral intubation. For male mice this dose was 195 or 97 mg/kg/day, but for female mice it was 299 or 149 mg/kg/day (time-weighted average dose over a 78-week period). Twenty mice of each sex were used as untreated controls, and an equal number were given the vehicle (corn oil) by oral intubation. As in the NCI rat study, gross necropsy was performed on each animal that died or was killed at the end, and similar histopathologic examinations were made.

Hepatocellular carcinomas occurred in all male mice (Table V-16), but only two were seen in females. The number of hepatocellular carcinomas in the high-dose male group were significantly greater than those in the control groups. The Cochran-Armitage test indicated a positive dose-response association with either the matched ($P = 0.025$) or the pooled ($P = 0.006$) controls. The Fisher exact test also yielded a significant ($P = 0.009$) comparison of the high-dose to the pooled control group.

A large number of alveolar/bronchiolar adenomas were also observed in the mouse study. They were present in 31% of the male (15/48) and female (15/48) high-dose mice. None occurred in the untreated or vehicle control males, and only one appeared in each female control group (Table V-17). The Cochran-Armitage test showed a significant ($P = 0.005$) positive dose-response association when either high-dose male or female groups were compared with appropriate untreated or vehicle control groups. The Fisher exact test also indicated that

TABLE V-16

Hepatocellular Carcinomas in 1,2-Dichloroethane Treated Mice

Group	Mice with hepatocellular carcinomas
Male	
Untreated controls	2/17 (12%)
Vehicle controls	1/19 (5%)
Low-dose group	6/47 (13%)
High-dose group	12/48 (25%)
Female	
Untreated controls	0/19 (0%)
Vehicle controls	1/20 (5%)
Low-dose group	0/50 (0%)
High-dose group	1/47 (2%)

Source: Adapted from NCI, 1978.

TABLE V-17

Alveolar/Bronchiolar Adenomas in Mice Treated with 1,2-Dichloroethane

Group	Mice with alveolar/bronchiolar adenomas
Male	
Untreated controls	0/17 (0%)
Vehicle controls	0/19 (0%)
Low-dose group	1/47 (2%)
High-dose group	15/48 (31%)
Females	
Untreated controls	1/19 (5%)
Vehicle controls	1/20 (5%)
Low-dose group	7/50 (14%)
High-dose group	15/48 (31%)

Source: Adapted from NCI 1978.

both high-dose groups had a significantly (p = 0.016) higher incidence rate than either of the control groups, but this test attributed no statistical significance to the incidence of alveolar/bronchiolar adenomas in the low-dose female mice.

Squamous-cell carcinomas of the forestomach occurred in ten of the mice treated with 1,2-dichloroethane and in two of the controls (Table V-18). The Cochran-Armitage test indicated a significant (P = 0.035) positive association between dosage and the incidence of these lesions when dosed female groups were compared with the pooled vehicle control, but the Fisher exact tests did not confirm this association.

TABLE V-18

Squamous Cell Carcinomas of the Forestomach in 1,2-Dichloroethane Treated Mice

Group	Mice with squamous-cell carcinoma of forestomach
Male	
Untreated controls	0/17 (0%)
Vehicle controls	1/19 (5%)
Low-dose group	1/46 (2%)
High-dose group	2/46 (4%)
Female	
Untreated controls	0/19 (0%)
Vehicle controls	1/20 (5%)
Low-dose group	2/50 (4%)
High-dose group	5/48 (10%)

Source: Adapted from NCI, 1978.

A statistically significant positive association between dosage and the incidence of mammary adenocarcinomas in female mice was also reported. These malignancies occurred in 18% (9/50) of the low-dose mice (P = 0.001, Cochran-Armitage test; P = 0.039, Fisher exact test) and 15% (7/48) of the high-dose mice (P = 0.003, Cochran-Armitage test). No adenocarcinomas of the mammary gland occurred in either the pooled vehicle controls (0/60) or the matched vehicle controls (0/20) (NCI, 1978).

To summarize, the NCI study indicated statistically significant association between oral intubation exposure to 1,2-dichloroethane and the incidence of alveolar/bronchiolar adenomas in both male and female mice. The study also established a statistically significant relationship between oral intubation exposure and the occurrence of hepatocellular carinomas in male mice. No such relationship was found for female mice, nor was an unequivocal association found between oral intubation exposure to 1,2-dichloroethane and the occurrence of squamous-cell carcinomas of the forestomach in either male or female mice.

The NCI bioassay had some major experimental design flaws. The rats treated with 1,2-dichloroethane and the vehicle control rats were housed in the same room as other rats intubated with 1,1-dichloroethane, dibromochloropropane, trichloroethylene and carbon disulfide. Untreated control rats were housed in a different room along with other rats intubated with 1,1,2-trichloroethane and tetrachloroethylene (NCI, 1978).

All mice used in the 1,2-dichloroethene study were housed in the same room as other mice intubated with 1,1,2,2-tetrachloroethane, chloroform, allyl chloride, chloropicrin, dibromochloropropane, 1,2-dibromoethane, 1,1-dichloroethane, trichloroethylene, 3-sulfolene, iodoform, methylchloroform, 1,1,2-trichloroethane, tetrachloroethylene, hexachloroethane, carbon disulfide, trichlorofluoromethane and carbon tetrachloride (NCI, 1978).

The high dose rats showed a significant dose-related increase in mortality ($P < 0.001$). The results were skewed particularly because the vehicle control had a greater mortality than low dose males early in the study. High dose male rat survival was low, 50% dead by week 55 and 89% dead by week 75 (Table V-12).

The rats, in general, appeared to suffer from chronic murine pneumonia ranging from 70% in high dose females to 95% in vehicle control females. Male rats appeared to have some hematopoietic system effects as observed primarily in the spleen: 16% and 12% in low and high-dose male rats, respectively, vs. 5% in vehicle controls. The female rats had 12% and 40% in the low and high-dose, respectively, vs. 10% in vehicle controls. In males, 12% of the low-dose and 16% of the high-dose vs. 0% in the vehicle controls had adverse circulatory system effects. The females had 6% and 16% adverse effects in the low and high-dose, respectively. In the liver, excluding fatty metamorphosis, there were 8% and 14% adverse effects in the high and low dose, respectively, vs. 0% in the vehicle controls for males and 8% and 16% in the high and low-dose, respectively, vs. 5% in the vehicle controls for females.

There were reported endocrine effects in the male rat of 14% and 16% in the low and high dose respectively vs. 0% in the vehicle controls.

The mice also suffered from chronic murine pneumonia. The untreated and vehicle controls, even though housed in the same room, did not suffer from pneumonia.

In the female mouse, the integumentary system, 14% and 6% with low and high dose, respectively, was affected. At the high dose, the urinary bladder (10%) was affected.

A carcinogenic bioassay of 1,2-DCE by inhalation was carried out by Maltoni, et al. (1980). Four groups of 180 Sprague-Dawley rats and four groups of Swiss mice of both sexes were exposed to four 1,2-DCE concentrations: 250-150 ppm, 50 ppm, 10 ppm, 5 ppm or 0 ppm respectively, for 7 hours daily, 5 days a week, for 78 weeks. The 250 ppm exposure had to be reduced to 150 ppm after several days because of severe toxic effects on the animals, particularly the mice. Two groups of 180 rats and one group of 249 mice served as controls. At the end of the exposure period, the animals were allowed to live until spontaneous death. No specific types of tumors were found in treated animals of either species. No relevant changes in the incidences of tumors normally occurring in the Sprague-Dawley rats, apart from a non dose-correlated increase in mammary tumors when compared with the controls. This was due to enhanced numbers of fibromas and fibroadenomas as opposed to malignant tumor types.

On the basis of data gathered to date, it appears that 1,2-dichloroethane is an animal carcinogen when administered by the oral route. No significant increase in the incidence of tumors has been observed in animals exposed via inhalation. Several explanations have been proposed to reconcile these apparent discrepancies, such as a difference in responsiveness by the strains of test animals studied and the route of exposure affecting the carcinogenicity of the substance.

There are several studies reported in the literature which demonstrate covalent binding of 1,2-dichloroethane to macromolecules, including DNA (Banerjee and Van Duuren, 1979; Guengerich, et al., 1980; DiRenzo, et al., 1982). The work of Banerjee and Van Duuren was designed to determine if 1) 1,2-DCE interacts with microsomal proteins of the liver, its principal target organ in the mouse, 2) if it binds to DNA in the absence or presence of microsomes and 3) if a correlation can be shown between binding and carcinogenicity. Microsomal protein preparations were obtained from young B6C3F1 mice. DNA was isolated from salmon sperm. Each preparation was incubated individually with [^{14}C] 1,2-DCE in the presence of native or denatured hepatic microsomes (2 mg protein) from male B6C3F1 mice. No detectable radioactivity was measured in preparations utilizing denatured microsomes, but considerably binding was observed to both liver microsomal proteins (19,000 ± 2,300 dpm/mg protein) and to sperm DNA (570 ± 2 dpm/mg protein) in the presence of the native microsomal preparation.

Banerjee and Van Duuren (1979) also did comparative _in vitro_ studies with hepatic microsomal protein preparations from B6C3F1 mice and Osborne-Mendel rats. The results can be seen in Table V-19. Hepatic microsomal protein from mice bound eight and six times more 1,2-DCE than did microsomal protein from male and female rats, respectively. This result is statistically significant for both the males and females of these species ($P < 0.001$). The covalent binding of [^{14}C] 1,2-DCE was five times greater to DNA in the presence of microsomes from male B6C3F1 mice than in the presence of microsomes from male Osborne-Mendel rats, whereas 1,2-DCE was bound 2.5 times greater to DNA in the presence of microsomes from female mice than from female rats. This result was also statistically significant: $P < 0.001$ for males and $P < 0.02$ for females. These observations are similar to those reported earlier by the same authors for trichloroethylene (Banerjee and Van Duuren, 1978). In both studies, significantly greater binding of ^{14}C-compound was noted in the target organ proteins of mice which are susceptible to compound-induced hepatocellular carcinoma than for Osborn-Mendel rats which are resistent to liver carcinoma by TCE or 1,2-DCE. These observations lend support to the hypothesis that a correlation exists between binding to DNA and the compound-induced carcinogenicity.

TABLE V-19

In vitro Binding of EDC to Hepatic Microsomal Protein from $B6C3F_1$ mice and Osborne-Mendel Rats and to Salmon Sperm DNA

Species	$[^{14}C]$EDC bound to macromolecules[a]			
	nmole/mg protein		nmole/mg DNA	
	male	female	male	female
B6C3F1 mice	1.75±0.15	1.23±0.17	0.05±0	0.05±0
Osborne-Mendel rats	0.22±0.04	0.21±0.03	0.01±0	0.02±0

[a] The results for mice are the average ±SD of 3 males and 3 females; the results for rats are the average ±SD of 7 males and 5 females. Three analyses were performed for each animal.

(Modified from Banerjee and Van Duuren, 1979).

Similar studies have been conducted by Guengerich, et al. (1981) in Sprague-Dawley rats. Microsomal and cytosolic fractions of liver homogenates were prepared from phenobarbital-treated males. Little irreversible binding of 1,2-DCE to the microsomal preparations was observed in the absence of NADPH; irreversible binding was linear with respect to time over the 90 minute testing period in the presence of NADPH. Liver microsomes catalyzed the NADPH dependent metabolism of 1,2-dichloroethane to metabolites irreversibly bound to calf thymus DNA. Cytosolic fractions also catalyzed binding of the compound to DNA in a reaction enhanced by GSH. Both reactions were linear with respect to time for 150 minutes of incubation. Pretreatment of rats with phenobarbital increased microsomal rates of total non-volatile product formation two-fold and irreversible binding to protein four-fold, but did not significantly affect covalently binding to DNA.

DiRenzo, et al. (1982) also showed that *in vitro* covalent binding to calf thymus DNA by 1,2-dichloroethane occurred following activation by hepatic microsomes isolated from phenobarbital-treated rats (strain not named). The degree of binding to form a DBA-adduct was considerably lower for 1,2-DCE than for most of the other compounds tested (see Table V-20). This could be due, in part, to the fact that only a relatively small fraction of 1,2-DCE is metabolized to active metabolites by the microsomal fraction. The greater conversion occurs in the presence of the cytosolic

TABLE V-20

Microsomal Bioactivation and Covalent Binding of Aliphatic Halides to Calf Thymus DNA

Aliphatic halides	Binding to DNA*
1,2-Dibromoethane	0.52±0.14(6)
Bromotrichloromethane	0.51±0.18(6)
Chloroform	0.46±0.13(6)
Carbon tetrachloride	0.39±0.08(6)
Trichloroethylene	0.36±0.14(7)
1,1,2-Trichloroethane	0.35±0.07(7)
Dichloromethane	0.11±0.05(6)
Halothane	0.08±0.01(6)
1,2-Dichloroethane	0.06±0.02(6)
1,1,1-Trichloroethane	0.05±0.01(3)

*nnol bound/mg DNA/h. Values are the mean ± standard deviation for the number of experiments in parentheses.

(Modified from DiRenzo, et al., 1982)

fraction. Thus, proportoinately less active metabolite would have been available with which adducts with DNA would be formed.

MUTAGENICITY

There are a number of studies which demonstrate a positive correlation between mutagenicity and carcinogenicity (Ames, 1979). In addition, there is evidence accumulated in mammals that most environmental carcinogens require bioactivation. Therefore, the identification of carcinogens by mutagenicity tests may be largely dependent upon the particular test system which is used. Table V-21 shows the results obtained with 1,2-dichloroethane in a number of short-term test systems.

1,2-Dichloroethane was shown to inhibit the growth of DNA polymerase-deficient Escherichia coli (P01A$^-$) (Brem, et al., 1974). E. Coli bacteria which are deficient in the enzyme DNA polymerase are sensitive to the inhibitory actions of chemicals which attack cellular DNA because they are unable to repair damage to their DNA.

In the bacterium Salmonella typhimurium, 1,2-dichloroethane produced a dose-dependent, although relatively weak, direct mutagenic effect in standard mutagenicity tests (Brem, et al., 1974; Simmon, et al., 1978). However, when further studies were undertaken, 1,2-dichloroethane was found in most of them to be activated to a highly mutagenic metabolite, when metabolized by enzymes in the soluble fraction (S-9) of the rat liver cell. (Kanada and Uyeta, 1978; Rannug, et al., 1978; Rannug and Beije, 1979). In addition, the mutagenic

TABLE V-21

Results of 1,2-Dichloroethane in Short-term Assys

Assay System	Effect* Measured	Results	References
A. Prokaryotic Mutagenesis:	G		
Salmonella		Weakly +	Brem, et al., 1974
"		highly + (activated)	Rannug and Beije, 1979
"		+ (with S-9)	Kanada and Uyeta, 1978
"		+ (TA 100)	Simmon, et al., 1978
"		+ (with activation)	Guengerich, et al., 1980
"		- (with induced S-9)	King, et al., 1979
"		+ (with S-9)	McCann, et al., 1975
"		+ (with S-9 ± GSH)	Rannug, et al., 1978
E. Coli, PolA$^+$/PolA$^-$		- (no S-9)	Brem, et al., 1974
"		- (with/without S-9)	Brem, et al., 1974
Lysis K39(a)		-	Kristofferson, 1974 (abstract - no details available)
B. Drosophila	G		
sex-linked recessive lethal test (larvae and adults)		+	Rapoport, 1960
		+ (lethal mutation)	Shakarnis, 1969
		+ (eye-color marker)	Nylander, et al., 1978
		+	King, et al., 1979

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* G = genotoxic; NG = non-genotoxic

+ = positive; - = negative

(Table V-[illegible] continued)

Assay System	Effect* Measured	Results+	References
C. DNA Binding	G		
		+ (*In vitro*, naked Calf thymus DNA, with NADPH + S-9)	Guengerich, et al., 1980
		+ (*In vitro*, naked with calf thymus DNA, NADPH + cytosolic fraction)	
		+ (minor covalent binding to naked calf thymus DNA with S-9)	DiRenzo, et al., 1982
		+ (Covalent binding to DNA)	Banerjee and VanDuuren, 1979
D. Barley kernels	G		
		+(increased #'s of recessive lethal mutations)	Ehrenberg, et al., 1974
E. *Saccharomyces cerevisiae*	MC?	Weakly +	Simmon, unpublished (cited in Simmon, 1980)
F. Mouse micronucleus test	MC	-	King, et al., 1979
G. *Allium* root tip	MC	-	Kristofferson, 1974 (abst.) (no details available)
H. Pulmonary adenoma induction in Strain A mice		-	Theiss, et al., 1977

metabolite was assumed to be a glutathione conjugate, which when synthesized and tested was highly mutagenic (Rannug and Beije, 1979; Guengerich, et al. 1980). This was surprising because compounds which are conjugated with glutathione are usually considered to be rendered less reactive and quickly and harmlessly excreted from the body. However, in this case, displacement of one reactive chlorine group by glutathione actually causes the other chlorine to become more reactive, and the compound formed is highly mutagenic. Also, a synthetic glutathione conjugate of this type was demonstrated to be directly mutagenic.

In other investigations of its mutagenic activity, 1,2-dichloroethane produced single-strand breaks in DNA of hamster cells and chromosomal aberrations in barley kernels (Ehrenberg, et al., 1974). The mutagenic effectiveness of 1,2-dichloroethane was reported to be 100 times greater than expected from the frequency of initial reactions with DNA. Displacement of a chlorine is thought to result in this amplification of effectiveness.

These findings concur with those indicating that displacement of one chlorine by glutathione, as shown by Rannug and co-workers 51978) leads to a more reactive derivative.

1,2-Dichloroethane has also been shown to be mutagenic in *Drosophila melanogaster* (Rapoport, 1960; Nylander, et al. 1978; King et al., 1979). Nondisjunction and recessive sex-linked lethal mutations were induced in *Drosophila* treated with 1,2-dichloroethane through their food supply (Shakarnis, 1969). A high frequency of mutations was also produced in a sex-linked genetaically unstable Drosophila system (Nylander, et al, 1978). Mutation was measured by the frequency of somatic mutations for eye pigment. Metabolic activity in Drosophila was suggested.

The synthetic reaction product of 1,2-dichloroethane and cysteine is a relatively strong mutagen in Drosophila and in Arabidopsis, as well as in Salmonella typhimurium (Rannug et al., 1978).

Other possible metabolites of 1,2-dichloroethane, chloroethanol and chloracetaldehyde, are highly mutagenic. Chloracetaldeyde is a direct-acting mutagen in Salmonella (McCann et al., 1975).

VI. HEALTH EFFECTS IN HUMANS

General

1,2-Dichloroethane is toxic to humans when it is ingested, inhaled or absorbed through skin or mucous membranes (Sax, 1975). The primary effects of acute or chronic exposure to 1,2-dichloroethane are central nervous system depression, gastrointestinal upset and injury to the liver, kidneys, lungs, and adrenals (Irish, 1963).

Acute Toxicity

Oral ingestion of 1 or 2 ounces, about 400 to 800 mg/kg body weight, of 1,2-dichloroethane by an adult male is fatal (NIOSH, 1978). Clinical symptoms of acute 1,2-dichloroethane poisoning by ingesion usually appear within 2 hours after exposure. Typicaly, they include headache, dizziness, general weakness, ausea, vomiting of blood and bile, dilated pupils, heart pain and constriction, pain in the epigastric region, diarrhea ad unconsciousness. Pulmonary edema and increasing cyanosi often are observed. If exposure is sufficiently brief these symptoms may disappear when the individual is no lnger exposed (Wirtschafter and Schwartz, 1939; McNally and ostvedt, 1941). However, persistent effects occur withsufficient exposure. Autopsies frequently reveal hyperemia ad hemorrhagic lesions of vital organs, especially the stomach, intestines, heart, brain, liver and kidney. Not all instances of 1,2-dichloroethane ingestion are fatal, but death has resulted in the majority of reported cases. Most often these deaths were attributed to circulatory and respiratory failure (Budanova, 1965; Yodaiken and Bancock, 1973; Luzhnikov et al., 1976; Zhizhonkov, 1976). Hypermia and hemorrhaging into the tissues of the visceral organs and lungs is often revealed at autopsy (Martin et al, 1969; Yodaiken and Babcock, 1973; Bryzhin, 1975). The symptoms described here observed in humans, including a prolonged latent period in certain of the clinical manifestations and delayed death, as well as the autopsy findings, are supported by animal data.

Exposure to 4000 ppm of 1,2-dichloroethane vapor for 1 hour produces serious illness in humans (Association of the Pesticide Control Officials, Inc., 1966). However, two men exposed experimentally in 1930 to 1200 ppm of 1,2-dichloroethane for 2 minutes apparently suffered little discomfort, except that the odor of 1,2-dichloroethane was extremely noticeable (Sayers et al., 1930). The effects of acute exposure by inhalation are similar to those described for ingestion, but the primary target appears to be the central nervous system (Patterson et al., 1975). Neural depression increases with the amount of 1,2-dichloroethane absorbed (Stewart, 1967). Damage to the liver, kidneys and lungs also occurs; reports of leukocytosis and elevated serum bilirubin are common.

The absorption of 1,2-dichloroethane through skin produces effects similar to those reported for inhalation.

but large doses are required to cause serious systemic poisoning.

Brief contact of 1,2-dichloroethane with skin seldom causes serious difficulties; however, repeated or prolonged contact results in extraction of normal skin oils and can cause cracking (Wirtschafter and Schwartz, 1939; Duprat, et al., 1976). Although pain, irritation and lacrimation normally occur when 1,2-dichloroethane contacts eye tissue, significant damage usually occurs only if the compound is not promptly removed by washing (Irish, 1963).

Chronic Toxicity

Few reports of chronic ingestion of 1,2-dichloroethane were found, but a few reports of repeated exposures to low concentrations of 1,2-dichloroethane by inhalation or skin absorption have been published. Chronic exposures to 1,2-dichloroethane by inhalation or absorption usually result in progressive effects that closely resemble the effects described for acute exposure, especially neurological changes, loss of appetite, gastrointestinal problems, irritation of the mucous membranes and liver and kidney impairment. The concentrations and exposure times associated with the onset of chronic symptoms in humans are difficult to deduce from the existing literature. In general, low level exposures of 10 to 100 ppm for durations of a few days to a few months appear to be characteristic of most reports. Fatalities may occur following such exposures, but they are more frequently associated with acute rather than chronic poisonings (Irish, 1963).

In addition to the above, information concerning biochemical changes and microscopic lesions resulting from exposure to 1,2-dichloroethane is increasing (Yodaiken and Babcock, 1963; Bonitenko, 1974). Unfortunately, the available information concerning the toxicology of 1,2-dichloroethane in humans is concerned with poisoning at higher concentrations or doses (NIOSH, 1978). The more subtle toxic effects which may result from chronic low level environmental exposure have not been reported. Of particular interest is the accumulation of 1,2-dichloroethane in the body with chronic low level exposure, which is suggested from the water/air, blood/air, olive oil/air, olive oil/water, and olive/oil blood partition coefficients (Morgan, et al, 1972; Sato and Nakajima, 1979). 1,2-Dichloroethane does concentrate in milk (Urosova, 1953; Sykes and Klein, 1957). More studies are required to gather information related to chronic low level exposures.

Sice 1,2-dichloroethane is both water soluble and lipid soluble, disposition after lung absorption of 1,2-dichloroethane in the body is widespread, and hence the toxic effects are related to virtually every organ system. The toxic consequences which have been seen in human subjects exposed to 1,2-dichloroethane vapors are similar to those seen following ingestion and include: cardiovascular disorders with increased heart rate, fluctuations in blood pressure, changes in blood components and damage to the myocardium, a characteristic narcotic effect on the central nervous system with nausea, vomiting, headache, dizziness, unsteady gait, dilated pupils, pathological reflexes, unconsciousness and coma, changes in the gastrointestinal tract with gastroenteritis, chest and stomach pains, cyanosis and pulmonary edema, damage to kidney function and signs of liver damage (Wirtschafter and Schwartz, 1939; Gaurino, et al, 1959).

Autopsy findings in fatal cases following acute poisoning include extensive bleeding into the tissues of all organs, inflammation, congestion, degeneration and necrosis in the liver, hemorrhaging of respiratory mucosa, hemorrhaging, swelling and inflammation of the lungs, degeneration of the myocardium, and hemorrhaging, inflamation and swelling of the kidney (Brass, 1949; Troisi and Cavallazi, 1961).

Odor is not a dependable guide for avoiding dangerous chronic exposures to 1,2-dichloroethane. Although some individuals can detect as little as 3 ppm under laboratory conditions, others consider it barely detectable at 50 or 100 ppm (Hoyle, 1961; Verschueren, 1977). The odor of 1,2-dichloroethane is generally considered unmistakable at 180 ppm, but even at this concentration, it may not be considered unpleasant. In addition, it is easy to become adapted to odor at low concentrations (Irish, 1963).

Poisoning Incidents and Case Histories - More than 100 cases histories of fatal and non-fatal 1,2-dichloroethane poisonings have been reported in some detail in the literature. In almost all cases involving ingestion of 1,2-dichloroethane (approximately 30), death resulted. The amounts of 1,2-dichloroethane consumed by the victims varied from "one sip" to 100 ml or more. Age varied from 1.5 years to about 80. Signs and symptoms included: violent vomiting, nausea, collapse and unconsciousness. Death usually occurred within two days of exposure, but, in a few instances, it was delayed up to six days.

More than 70 cases of acute inhalation exposures to 1,2-dichloroethane are described in the literature (see Table VI-1); only a small fraction of these, about 13%, resulted in fatalities. In general, acute inhalation exposures have been work-related and associated with the use of end products containing 1,2-dichloroethane. Most fatalities have been adult males. Symptoms and signs associated with acute inhalation exposures are generally similar to those previously described. In lethal exposures by inhalation, death does not occur as rapidly as in lethal exposures by ingestion. However, most victims succumb within two weeks.

Among recorded case histories, most victims of acute inhalation poisoning recovered and were released as clinically normal a few days after exposure. Only a few follow-up

TABLE VI-1

Cases of Fatal 1,2-Dichloroethane Ingestion

Patient	Amount of Chemical taken into the body (if known)	Onset and Progression of symptoms	Reference
63-year-old man	2 onces	2 hours Nausea; faintness; vomiting; dazed; cyanotic: dilated pupils; coarse rales; weak, rapid pulse; dark brown liquid stools; increased cyanosis; pulse and heart sounds absent; dypspnea; death 22 hours after ingestion	Hueper and Smith, 1945
1-1/2-year-old boy	1 sip	Extreme weakness; comatose; vomiting; death the next day	Keyser, 1944
1-1/2-year-	Unknown	Coma; anuria; pneumonia	Meurs, 1944
4 males 20-29 years old	150-200 ml	3-4 hours Symptoms not reported; death 10, 15,33, and 35 hours after ingestion	Bryshin, 1945
53-year-old man	Unknown; maybe on several occasions	Inattentive; sleepy; excitement; unconsciousness; rapid, irregular breathing; cyanosis; completely dilated pupils; light pulse; heart and respiratory failure; lung edema; death at least 10 hours after ingestion.	Bloch, 1946

TABLE VI-1 (Continued)

Patient	Amount of Chemical taken into the body (if known)	Onset and Progression of symptoms	Reference
43 -year-old man alcoholic	4 drinks diluted with orange juice	Unconsciousness; death 8 hours after ingestion	Hulst, 1946
43-year-old man, alcoholic	4 drinks diluted with orange juice	Confusion; deep sleepiness; unconsciousness; vomiting with blood; death 24 hours after ingestion	Hulst, 1946
55-year-old man, asthmatic	20 ml	Epigastric pain; extreme dizziness; sleepnessness; vomiting; slow pulse; death 24 hours after ingestion	Roubal, 1947
16-year-old man	50 ml	Vomiting; epigastric pain; fourth day: muscle spasms, hiccups, pulse 108, no eyelid response to light; death 91 hours after ingestion	Stuhlert, 1949
Man	Unknown	Violent vomiting; painful visceral cramps; extreme weakness; pale, cyanotic; weak, rapid pulse; weak heart sounds; rales; dyspnea; increased cyanosis and dyspnea, and weakening pulse; death 20 hours after ingestion	Stuhlert, 1949

TABLE VI-1 (Continued)

Patient	Amount of Chemical taken into the body (if none)	Onset and Progression of Symptoms	Reference
Man	Unknown	Violent vomiting; circulatory failure and death 39 hours after ingestion	
50-year-old man	30 ml	30 minutes Unconsciousness; vomiting, cyanosis; dilated, fixed pupils; pulmocary edema, extreme dyspnea; death 10 hours after ingestion	Lochlead and Close, 1951
Man	About 20 ml	1 hour Collapse; repeated vomiting; after 12 hours blue lips, difficulty breathing; death 13 hours after ingestion	Flotow 1952
Man	About 20 ml	Death within 12 hours of ingestion	
30-year-old man	40 ml	Slight cough; reddened conjuctivae; shock; weak, rapid pulse (100); regained consciousness after 3 hours; hyperactivity alternating with semi-comatose condition; death 28 hours after ingestion	Garrison and Leadingham 1954

TABLE VI-1 (Continued)

Patient	Amount of Chemical taken into the body (if known)	Onset and Progression of symptoms	Reference
Man		2 hours Violentely ill; shock cyanosis; pulmonary edema; light coma; vomiting and diarrhea; low blood pressure; severe albuminuria; death at 19 hours after ingestion	Hubbs and Prusmack, 1955
2-year-old boy		2 hours Violently vomiting; 20 hours after ingestion; restlessness, cramps; death occurred approximately 21 hours after ingestion during convulsions	Durwald, 1955
79-year-old man	1 sip	Vomiting; weakness; pale, cyanotic; scarcely conscious; vagueness; rapid, regular pulse (136); blood pressure not measureable; died 40 hours after ingestion with heart and circulatory failure	Weiss, 1957
3-year-old boy	1 sip	Vomiting; diarrhea; tonic spasms; increasing loss of consciousness; dyspnea; impaired circulation; death 20 hours after ingestion	
23-year-	1 sip	1 hour Dizziness; nausea; unconsciousness; vomiting; cyanosis; no pupil reaction; no corneal reflex; difficult breathing; strong motor unrest; death after 8 hours due to respiratory and circulatory failure	Reinfried, 1958

TABLE VI-1 (Continued)

Patient	Amount of Chemical taken into the body (if known)	Onset and Progression of symptoms	Reference
63-year-old man	1 or 2 sips	Shortly after ingestion; unconsciousness; soon regained consciousness, strong vomiting; period of improvement; 10.5 hours after ingestion unconscious; blood pressure falling; 14 hours after ingestion death resulting from circulatory failure	Freundt et al. 1963
3 men, 19-27 years old	70, 80 and 100 ml	Few minutes Vomiting; weakness; dizziness; lost consciousness; deaths occurred 5-8 hours after ingestion	Kaira.
32-year-old man.	8 ml	Immediate Burning sensation in mouth throat, stomach; drank milk and vomited; weakness; speech retardation; lethargic; asthenic; cold sweat; heart sounds muffled; weak and rapid pulse; 22 hours after ingestion excitation, restlessness, delirium, face flushed, cyanosis, systolic murmur, respiratory depression, circulatory weakness, anuria, then death 56 hours after ingestion	Bogoyavlenski, et al. 1968
27-year-old man	Half a glass	2.5 hours unconsciousness; vomiting of dark vomitus; regained consciousness after 12 hours. Burning sensation in digestive tract; dyspnea; nausea; cyanosis; respiratory rate 32/minute; moist rales in lungs; heart sounds muffled, pulse 100, extrasystoles;	

TABLE VI-1 (Continued)

Patient	Amount of Chemical taken into the body (if known)	Onset and Progression of symptoms	Reference
80-year-old man	50 ml	Elevated serum enzymes—LDH, SGOT SGPT, alkaline phosphatease, glutamic dehydrogenase, RNAase; death a few hours after ingestion	Secchi et al. 1968
57-year-old man	40 ml	Somnolence; vomiting; sinus tachycardia (100); ventricular extrasystoles; return of consciousness 14 hours after ingestion dyspnea; loss of blood pressure; cardiac arrest; death 24 hours after ingestion	Martin et al. 1969
18-year-old man	50 ml	1 hour Somnolent; cyanotic; 4 hours later foul smelling diarrhea; 5.5 hours later shock of circulatory system; death after 17 hours in irreversible shock	Schoenborn et al. 1970
14-year-old boy	15 ml	Within 2 hours severe headache; staggering; lethargy; periodic vomiting; blood pressure drop; oliguric; increasingly dyspenic, somnolent and oliguric; ecchymoses; sinus bradycardia; cardiac arrest; pulmonary edema; refractory hypotension; death on 6th day	Yodaiken and Babcock, 1973

case studies have been made to determine if long-term effects develop from acute inhalation exposure to 1,2-dichloroethane. In a few poorly documented instances, chronic changes in the central nervous system appear to have persisted 1 to 18 years following exposure (Smirnova and Granik, 1970). In the most serious case, illness was accompanied by encephalitis and injury to the subcortical region that improved only slowly during 14 years. It is uncertain, however, that exposures were only to 1,2-dichloroethane. Further studies of delayed effects of acute inhalation exposures to 1,2-dichloroethane are needed.

Recent Studies

Since 1970, several comprehensive studies have been published which detailed the human toxicity of 1,2-dichloroethane in the acute as well as the chronic forms.

Summarized in Table VI-2 are the symptoms of acute 1,2-dichloroethane poisoning from ingestion in 118 patients and the clinical findings in these patients reported by Akimov et al. (1976, 1978). The amount of compound swallowed ranged from 20 to 200 ml. The patients were divided into three groups--mild, moderate, and severe--the severity of the symptoms do not necessarily correlate with the amount ingested.

TABLE VI-2

Symptoms and Clinical Findings of Acute Peroral 1,2-Dichloroethane Poisoining

(translated from Akimov et al., 1976, 1978)

Symptoms	Degree of severity of Poisoning			Total Number of Patients, absolute (%)
	Mild	Moderate	Severe	
Dichloroethane odor in mouth	17	10	81	108 (91)
Dry skin	15	10	64	89 (75)
Mucosal cyanosis	2	2	76	80 (67)
Respiratory disorders	3	4	63	70 (59)
Tachycardia	12	5	57	74 (62)
Arterial hypotension	3	4	81	88 (74)
Loss of consciousness	-	1	49	50 (42)
Mydriasis	6	10	69	85 (72)
Horizontal nystagmus	8	4	16	28 (23)
Speech disorders	4	6	15	25 (21)
Muscular hypotonia	2	4	52	58 (46)
Decrease in tendon reflexes	2	5	48	55 (46)
Presence of pathologic-reflexes	-	1	7	8 (6)
Convulsions	-	-	9	9 (7)

TABLE VI-2 (Continued)

Symptoms	Degree of severity of poisoining			Total Number of patients, absolute (%)
	Mild	Moderate	Severe	
Cerebellar disorders:				
Ataxia	8	7	18	33 (27)
Romberg's sign	9	9	21	39 (33)
Intention tremor	13	9	29	51 (43)
Adnodochokinesis	7	7	16	30 (25)
Dysmetria	5	4	11	20 (16)
Extrapyramidal disorders:				
Rare nictation	2	2	9	13 (11)
Hypomimia	4	5	19	28 (23)
Bradykinesia	3	4	11	18 (15)
Delirious hallucinations	1	1	2	4 (3)

The most common effects in mild to severe 1,2-dichloroethane poisoning were a pronounced odor on the patient's breath, cyanosis, difficulty in breathing, tachycardia, hypotension, mydriasis, loss of muscle tone and a decrease in tendon reflexes. Neurological syndromes involving disturbances in consciousness, mental disorders, cerebellar and extrapyramidal abnormalities were often noted (Table VI-3).

The neurological symptoms in mild poisoning disappeared 4 to 5 days after the onset. These disorders were more prolonged in moderate poisoning, and a cerebellar syndrome was observed for up to two weeks in some patients from this group. The neurological disorders in the group of patients who were severely poisoned were characterized by loss of consciousness, muscle hypotonia, a decrease in tendon and periosteal reflexes, the onset of pathological reflexes in the feet and convulsions. The cerebellar and extrapyramidal disorders, which lasted for 2 to 3 weeks, were more pronounced.

Shchepotin and Bondarenko (1978) described acute toxicity to 1,2-dichloroethane in 248 patients, males and females between the ages of 15 and 72. The majority of these patients (85 percent) suffered harmful effects resulting from oral ingestion of the liquid chemical, while toxicity followed inhalation of vapors in 15 percent. The length of inhalation of 1,2-dichloroethane was, on the average, 20 to 30 minutes. However, concentrations of the inhaled 1,2-dichloroethane vapors were not reported.

TABLE VI-3

Characteristics of the Basic Forms of Damage to the Nervous System in Acute Dichloroethane Poisoning

(translated from Akimov et al., 1978)

Severity of damage		
Mild	Medium	Severe
Euphoria	Deafness	Stupor, coma
Hallucinations	Hallucinations Psychomotor excitation	
Mild nystagmus	Mydriasis Persistent nystagmus	Mydriasis Persistent nystagmus Reduction of corneal reflexes
	Muscular hypotonia	Muscular hypotonia
Reduction of abdominal and sole reflexes	Reduction of abdominal and sole reflexes	Reduction of abdominal and sole reflexes
	Reduction of reflexes of extremities	Reduction of reflexes of extremities
—	—	Toxic convulsions
Moderate atactic symptoms	Pronounced atactic symptoms	Pronounced atctic symptoms
—	Hypomimia Bradykinesia	Hypomimia Bradykinesia
	Dysarthria	Dysarthria

Four main clinical syndromes were identified with 1,2-dicloroethane poisoning in these patients. The hepatic and cardiovascular systems were affected most often following central nervous system disorders. Renal dysfunction was also observed. Neurological disorders were noted in all patients. These included unconsciousness (narcotic effect) and respiratory inhibition via depression of the medullary center of the brain. A syndrome of acute cardiovascular insufficiency developed in 60 percent of the patients including arrhythmias and a fall in both systolic and diastolic blood pressure, with reduction of cardiac output and decreased peripheral resistance. In 35 percent of the patients, a syndrome of liver dysfunction was evident. The liver was enlarged, hyperbilirubinemia was severe, and serum albumin and asparagine transaminase activities were increased.

With inhalation poisoning, in particular, the kidneys were affected. This is explained by the relatively high arterial blood flow (20 percent of cardiac output) perfusing the kidneys. Nephropathology in these patients was manifested by oliguria, proteinuria, azotemia and acute renal failure with disturbances of acid base balance.

Of interest was a common syndrome of gastroenteritis not only in the patients poisoned by ingestion, but also in the patients poisoned by inhalation, although the degree of gastroenteritis was milder in those patients poisoned by inhalation.

Shchepotin and Bondarenko (1978) attempted to correlate the severity of 1,2-dichloroethane poisoning with the concentrations of 1,2-dichloroethane in blood and urine as determined by gas chromatography. While a severe clinical course of poisoning was sometimes noted with high concentrations in blood and urine, no correlation between severity and DCE levels in body fluids was established. Similarly, no direct correlation between severity of poisoning and the amount of 1,2-dichloroethane inhaled was evident.

Bonitenko (1974, 1977), in a description of 1,2-dichloroethane toxicity in 32 patients, compared the severity of clinical symptoms of poisoning with concentrations of the chemical in the blood. Coma was associated with blood concentrations of 15-30 mg percent, and the level at which consciousness returned corresponded to levels below 8-10 mg percent. The method of measurement was not described. These investigators determined at autopsy that the level in adipose tissue was 68 mg per 100 gm of tissue while the corresponding level in blood was only 1.2 mg percent.

Luzhnikov et al. (1970), in a study of a series of 110 patients, observed clinical symptoms similar to those reported by Akimov et al. Within the first hours following exposure, 77 percent of these patients demonstrated acute gastritis with vomiting, neurological disorders including coma (81 percent), acute cardiovascular insufficiency (57 percent), hepatitis (56 percent) with liver enlargement and functional abnormalities (abnormal bromosulfonphthalein clearance, plasma bilirubin and plasma glutamine-asparagine transaminase levels). Clinical symptoms of poisoning were observed with only minimal concentrations of 1,2-dichloroethane in the blood (0.5 mg percent). Coma developed at a blood concentration as low as 5 to 7 mg percent and higher. Gas-liquid chromatography was utilized to measure the concentration of 1,2-dichloroethane. Differences in analytical methodology may help to explain the apparent discrepancy in the values associated with development of coma given by Bonitenko and those reported by Luzknikov et al. Time of sampling may also affect the resulting concentration measurement.

Luzhnikov and co-workers (1974, 1976) also investigated the toxic effects of 1,2-dichloroethane on the myocardium in at least 160 patients. These workers developed a concept of "exotoxic shock," that is, hemodynamic shock due to the toxic effects of a chemical on the myocardium. During the compensatory phase of shock, total peripheral resistance was 15 to 25 percent higher than normal, arterial blood pressure was normal or increased slightly, while cardiac output and blood volume were decreased significantly. In decompensated shock, pronounced and progressive hypotension was observed, cardiac output was decreased 30 to 70 percent and peripheral resistance was either unchanged or slightly decreased. Electrocardiographic (ECG) changes including arrhythmias were observed in both compensated and decompensated shock.

In analyzing the myocardial function, definite changes in the cardiac cycle were found in the compensated shock phase: isometric contraction was decreased, expulsion time (ventricular emptying period) was increased, intraventricular pressure was increased and asynchronous contractions occurred. In the decompensated exotoxic shock phase, myocardial contractile force was markedly decreased during ventricular systole and prolonged periods of asynchronous contractions were observed. The authors noted that a 25-30 percent increase in peripheral resistance for a prolonged period will produce the observed left sided heart failure, especially after the observed kidney lesions appear as an additional contributing factor (Luzhnikov et al., 1974, 1975).

Morphological examination of the myocardium at autopsy showed significant edema in the cells of the capillary endothelium and stenosis of the capillary lumina. The micro-circulatory vessel changes also were accompanied by pronounced edema of the myocardial interstices with accumulation of polymorphonuclear leucocytes and microfocal hemorrhages. Histological examination showed a diminished presence of glycogen and degenerative changes of varying degrees in the cardiac muscle. Mitochondrial damage was indicated by a decrease in enzyme activities.

Toxicity in Infants and Children

1,2-Dichloroethane poisoning in children presents a clinical syndrome similar to that seen in adults. Hinkel

(1965), in Germany, reviewed seven cases of acute accidental poisoning in children ranging in age from 1 to 6 years, from an exposure to a "nerve balsalm" medicine which was 75 percent 1,2-dichloroethane. The features of clinical toxicity are summarized in Table VI-4. Within an hour after exposure, severe and persistent vomiting occurred. Immediately, or even after an interval of 10 to 12 hours, various degrees of narcotic effects were present. The symptoms ranged from somnolence to coma; less frequently, motor unrest, reflex increases and convulsions occurred. Indications of circulatory failure were also present. The manifestations of toxicoses in the child thus correspond to those observed in adults. The disturbances in kidney and liver function which are observed in the adult were less frequent in the children poisoned from the "nerve balsalm." However, corresponding investigations have not been undertaken in all instances. Tachycardia indicated that the effect of 1,2-dichloroethane on the heart was similar to that of chloroform, although no ventricular fibrillation was recorded. The blood changes were not exceptional. In particular, there was no leukocytosis or erythrocyte and hemoglobin increase which have been described by others. Electroencephalograms were not routinely performed; however, in the patients for which they were recorded, the EEG's proved to be normal. The gross and histopathological findings were the same as those described for 1,2-dichloroethane poisoning elsewhere in the literature.

TABLE VI-4

SUMMARIZATION OF THE CLINICAL SYMPTOMS IN CHILDHOOD
(adapted from Hinkel, 1965)

Cases	Appearance of the clinical symptoms	Gastrointestinal symptoms	CNS symptoms	Circulatory symptoms	Clinical interval	Blood picture	Liver & Kidney findings	Details
1.	immediately	severe vomiting	inconspicuous	circulatory insufficiency	not present	no findings	urine no findings	easy course
2.	1 hour	severe vomiting	unrest, sluggish pupil reaction	circulatory insufficiency	not present	no findings	urine no findings	easy course
3.	1/2 hour	Severe vomiting later diarrhea, pressure pain in abdomen, liver swelling	soporose to comatose	circulatory insufficiency	not present	—	—	exitus
4.	2 hours	severe vomiting	somnolent, reflex and tonus increase	circulatory insufficiency	not present	no findings	urine, no findings	survived
5.	immediately	severe uninterrupted vomiting	somnolent to soporose	circulatory insufficiency	12 hours	no findings	albuminuria, leukocyturia, retention of substances normally in urine	survived
6.	1 hour	—	somnolent to soporose	circulatory to sufficiency	12 hours	—	—	exitus
7.	1/4 hour	severe vomiting	staggered gait, somnolence	circulatory insufficiency	8 hours	leukocytosis with left displacement	no findings	survived

In spite of the fact that some of the characteristic changes of 1,2-dichloroethane poisoning were not present, the diagnosis of oral hydrocarbon intoxication was indicated.

The toxic lethal dose in children is less than for adults, ranging from 0.03 to 0.9 gm/kg. However, this oral dose level did not always cause death.

Infant exposure to 1,2-dichloroethane with subsequent toxic effects can occur via the milk of nursing mothers who heve been exposed to the compound. Urusova (1953) demonstrated the presence of 1,2-dichloroethane in the milk of nursing mothers who were exposed to the chemical by inhalation or cutaneous absorption in an industrial setting. Samples of breast milk and exhaled air from the lungs usually were taken immediately after work and at periods up to 2 1/2 hours after work exposure. 1,2-Dichloroetahne was found in the breast milk within 5 minutes after the ending of the work period, peaking 1 hour post work exposure. A similar pattern was found for breath analysis. A concentration of 1,2-dichloroethane in the work atmosphere was determined to be 0.063 mg/liter (0.016 ppm). After exposure to this atmospheric concentration for one hour, 0.58 mg/liter (0.014 ppm) was found in the expired air, and 0.54 to 0.64 mg percent was found in the breast milk. In many cases, 1,2-dichloroethane was detected in the mothers' milk 18 hours after work had ended. The concentration ranged between 0.2 to 0.63 mg percent, whereas the breath concentration of 1,2-dichloroethane was 0.009 to 0.017 mg/liter (0.002 to 0.004 ppm). 1,2-Dichloroethane was blown out of the milk by an air stream at the rate of 1 liter/hour with heating in a water bath to 50° and was concentrated in alcohol. The amount of dichloroethane was determined by Ginzburg's method. The exhaled air was collected through the exhalation valve of a gas mask. The dichloroethane was absorbed and concentrated in alcohol and determined by the same method.

1,2-Dichloroethane also has been found in cows' milk which provides another source for exposure in infants and young children (Sykes and Klein, 1957).

Microscopic Pathology and Cellular Toxicity

Within the last few years, increasing interest has been expressed in the toxic manifestations of 1,2-dichloroethane exposure at the cellular and biochemical levels. As noted above, Luzhnikov et al. have described the histological changes in myocardial tissue (1974, 1976). Yodaiken and Babcock (1973) described clinical features and pathologic findings in detail for a case of fatal poisoning. The significant abnormalities related to the liver, kidneys and adrenal glands. Microscopically, extensive liver parenchymal cell necrosis was found with only scattered vacuolated cells and occasional islets of surviving cells located near or around central veins and portal triads. Fat stains confirmed the presence of lipid in the vacuoles. The kidneys were yellow and swollen. The glomerulae were intact although focal epithelial cell necrosis was observed. Marked degenerative changes were found in the descending proximal limb and the thick ascending limb of the nephrons. Lipid staining showed extensive fat droplet accumulation most marked in cortical areas but present throughout the tubular structure. The adrenals microscopically showed vascular congestion and well-marked focal degenerative cell damage in all zones of the cortex. The prominent clinical chemistry before death was hypoglycemia and hypercalcemia (Yodaiken and Bancock, 1973).

Schoenborn et al. (1970) found disseminated intravascular coagulation in a single acute fatality of 1,2-dichloroethane poisoning. But, unlike Martin's observations in 1968, this patient did not show an increased tendency to bleed.

Luzhnikov et al. (1974) studied the coagulability of blood in 30 patients. In 1,2-dichloroethane poisoning, they found an increased amount of heparin in the blood. Also observed was an increase in fibrinolytic activity, a prolonged clotting time and an increased prothrombin index, all of which are in accord with hemorrhaging or increased tendency toward hypocoagulation.

Bonitenko et al. (1974, 1977) have shown that the leucocyte count in the blood of patients poisoned with 1,2-dichloroethane increases as a function of severity of poisoning (see Table VI-5). In addition, increases in serum aminotransferase enzyme activities correlates with severity of poisoning (Table VI-6). These latter effects are related

TABLE VI-5

Mean Number of Leukocytes in the Blood as a Function of the Severity of the 1,2-Dichloroethane Poisoining

(Bonitenko et al., 1977)

Degree of poisoning	Mean $\bar{x}$	Std. Dev. m
Mild	6800	240
Moderate	9200	330
Severe	12000	360

TABLE VI-6

Mean Serum Aminotransferase Values in the Early Stages of 1,2-Dichloroethane Poisoning (U per ml)

(Bonitenko et al., 1977)

Degree of poisoning	Alanine-aminotransferase (SGOT)		Aspartate-aminotransferase (SGPT)	
	mean $\bar{x}$	Std dev m	mean $\bar{x}$	Std. Dev. m
Mild	39	4.9	32.7	5.2
Moderate	62	7.1	50.2	7.3
Severe	117	12.5	107	13.2

to organ damage, particularly to damage in the liver. The blood leucocyte and serum enzyme activity provide a means of early evaluation of the degree of 1,2-dichloroethane poisoning and institution of appropriate therapy.

Epidemiology - The earlier available reports of chronic exposure to 1,2-dichloroethane are complicated by concurrent exposure of the subjects to other organic chemicals. Hence the description of observed toxic effects encountered in these reports cannot be ascribed entirely to 1,1-dichloroethane. These reports may, however, have certain value in suggesting the synergistic toxicities which may occur with simultaneous multi-chemical exposure, and are, therefore, summarized below.

Forty-eight cases of poisoning in Italy by a fumigant mixture of 75 percent 1,2-dichloroethane and 25 pecent carbon tetrachloride were reported by DiPorto and Padellaro (1959). Mild, moderate and severe pathological syndromes were described. Central nervous system effects and gastrointestinal disorders were seen commonly in these patients. The effects were mild for 28, moderate to severe for 16 and fatal for 4 persons. Clinical findings included acute hepatorenal insufficiency with the implications associated with this syndrome. In addition, necrotic and hemorrhagic lesions in the liver, primarily in the centrolobular cells, necrosis of the tubular epithelium in the kidneys, as well as proliferative changes in the glomeruli including multinucleated cells, were found in the fatal cases.

In the same year, Cetnarowicz (1959) published a study of Polish workers employed by an oil refinery that used a 4:1 mixture of 1,2-dichloroethane and benzene as a processing fluid. After a two- to eight-month exposure to 10 to 200 ppm 1,2-dichloroethane in the work site air, 16 workers on one shift experienced a general reduction in body weight of 2 to 10 kg; four had tender, slightly enlarged livers, seven had tenderness of the epigastrium and most had elevated urobilinogen levels in the urine. Thirteen of the workers had normal levels of erythrocytes and hemoglobin, but only nine showed a normal distribution of white blood cells. Other workers had abnormal levels of serum bilirubin, albumin, globulin, fibrin and blood non-protein nitrogen. In general, about half of the workers had some loss of liver function, and nearly one-third experienced changes in the gastrointestinal tract, sinus bradycardia or hematopoietic system. It should be noted, however, that some of the reported blood changes could reflect benzene poisoning rather than 1,2-dichloroethane poisoning.

Khubutiya (1964) studied hematologic changes in an unspecified number of 1,2-dichloroethane workers. Blood cell morphology, color index, red blood cell count and hemoglobin content were recorded. Samples from about one-third of the workers contained hyperchromic erythrocytes without megaloblasts. Nearly half of the blood samples showed moderate to high sedimentation rates induced by an increase in blood globulin. Leukopenia with relative and absolute neutrophilia and absolute lymphopenia was noted. Moderate or marked monocytosis was frequently observed. Turk's cells occurred in the peripheral blood of one worker in five. The number of platelets was frequently reduced. Khubutiya attributed both the monocytosis and the Turk's cells to stimulation of the reticuloendothelial system by long, unspecified exposures to 1,2-dichloroethane.

Brzozowski et al. (1954) reviewed the health status and work practices of Polish agricultural workers who used 1,2-dichloroethane as an insecticide. The liquid was brought to the field in barrels and was then poured by hand into a series of holes. Skin absorption, which resulted from spillage on clothes and shoes, was probably as significant a contribution to exposure as inhalation. Air concentrations of 1,2-dichloroethane were estimated at 15 to 60 ppm. Signs and symptoms of exposure were reported in 90 of 118 workers. The most common subjective complaints were conjunctival congestion, reddening of the pharynx, bronchial symptoms, metallic taste in the mouth, headache, weakness, nausea, abdominal and epigastric pains, tachycardia, dyspnea after effort and burning and reddening of skin. Liver function tests were significantly abnormal in 70 percent of those tested.

No changes were found in the blood or functions of internal organs of 100 factory workers exposed to 1,2-dichloroethane for six months to five years at concentrations of 25 ppm or less (Rozenbaum, 1947). However, functional disturbances of the nervous system occurred in several workers, including heightened lability of the autonomic nervous system, diffuse red dermatographism, muscular swelling, bradycardia and increased sweating.

Kozik (1975) reported a study of a group of workers in a Russian aircraft industry chemically exposed to 1,2-dichloroethane during the manufacture of soft rubber tanks. He compared findings in this group to those for the workers in the entire factory. He looked at morbidity and temporary loss of ability to work for the two groups.

Concentrations of 1,2-dichloroethane varied from 5 to 40 ppm and persisted for 70% to 75% of the working time of the exposed group. Total morbidity, acute gastrointestinal disorders, neuritis, radiculitis and other diseases were generally more pronounced among workers exposed to 1,2-dichloroethane than among other workers in the factory. Among 83 exposed workers, 19 were found to have diseases of the liver and bile ducts, 13 had neurotic conditions, 11 experienced autonomic dystonia, 10 had goiter or hyperthyroidism and 5 reported asthenic conditions.

No epidemiological studies of 1,2-DCE other than in industrial exposures have been reported.

VII. MECHANISMS OF TOXICITY

The cellular mechanisms of toxicity of 1,2-dichloroethane remain to be investigated. However, a few generalizations may be made. 1,2-DCE causes acute toxicity via direct effects on the central nervous system (CNS). The morphological evidence shows that 1,2-DCE produces adverse effects on the lungs, liver, heart, adrenals and kidneys.

The signs and symptoms of acute toxicity of 1,2-DCE vary depending on the species, route of administration and concentration or dose. Depending upon the intensity of the exposure and the species of the animal, the liver may show fatty degeneration or slight congestion with slight parenchymal degeneration. The kidney often shows signs of moderate inflammatory irritation with moderate exposure, but with more severe poisoning, tubular damage ranges from slight parenchymal degeneration to complete necrosis with interstitial edema, congestion and hemorrhage. Plaa and Larson (1965) observed an increase in urinary protein due to the nephrotoxic effect of 1,2-DCE.

When administered perorally, 1,2-DCE produces direct irritation of the gastrointestinal tract with cellular mucosal damage, probably due in part to the solubility properties of the chemical (Parker, et al., 1979). Kistler and Luckhardt (1929) found hemorrhages in the mesentery and in the intestinal mucosa. Pre-neoplastic and malignant lesions of the gastrointestinal tract were observed in rodents exposed to 1,2-DCE by gavage in the NCI bioassays (NCI, 1978).

Pulmonary congestion and edema are very frequent findings whether the exposure to 1,2-DCE is by inhalation or orally (Parker, 1979). Like chloroform, 1,2-DCE may have direct effects on the functional properties of the heart. Heppel, et al. (1945, 1946) and Hofmann, et al. (1971) observed fatty degenerative changes in the myocardium of the guinea pig after inhalation exposure.

Metabolite Toxicity and Protection

The 1,2-dichloroethane metabolites, chloroacetaldehyde, chloroethanol (oral LD_{50} for rats - 95 mg/kg), and chloroacetic acid (oral LD_{50} for rats - 76 mg/kg) are several times more toxic than dichloroethane itself (oral LD_{50} for rats - 770 mg/kg) (Woodward et al., 1941; Heppel et al., 1945, 1946; Ambrose, 1950; Hayes et al., 1973). Johnson (1967) suggests that chloroacetaldehyde may be the toxic metabolite, since this very reactive compound is capable of both enzymatic and non-enzymatic interaction with cellular sulfhydryl groups. However, Yllner (1971a, b) found that chloroacetic acid also reacted extensively with sulfhydryl compounds *in vivo*. Heppel, et al. (1945, 1946) found a high mortality (35 percent) in rats given 1.3 g/kg of 1,2-DCE orally. Mortality was reduced by pre- or post-administration of methionine, cysteine, cystine and other sulfhydryl compounds. Sulfur-containing amino acids, cystine and methionine, also protected young rats from inhalation exposure. This protective effect of sulfhydryl compounds is clearly related to the marked depletion of glutathione levels that occurs in the livers of rats given 1,2-dichloroethane, chloroethanol or chloroacetaldehyde (Johnson, 1965, 1967).

Johnson (1965, 1966, 1967) observed that, within 2 hours, a single oral dose of 1,2-dichloroethane (4 millimoles/kg) reduced the level of liver glutathione in rats to 52% of that in controls. 2-Chloroethanol (0.67 millimole/kg) similarly lowered glutathione levels to 17% of control values with formation of S-carboxymethylglutathione. Reduction of liver glutathione may have serious toxicological consequences because the liver is more susceptible to injury in the absence of this compound (Hayes, 1975).

Johnson (1965, 1967) also noted that the morbidity and mortality of young rats given chloroethanol orally was reduced by concomitant administration of ethanol. He postulated that the protective effect of ethanol was due to simple substrate competition for alcohol dehydrogenase which catalyzes the conversion of chloroethanol to chloroacetaldehyde. Ethanol also inhibited early effects of chloroethanol on liver glutathione depletion in these animals. This author suggests also that the minimal toxicity observed with chronic low inhalation doses of dichloroethane in different animal species by Heppel et al. 1946) may be explained simply by the rapid replenishment of tissue glutathione.

Over the past several decades, scientists have conducted a great deal of research in an effort to establish the mechanism(s) by which chemical substances exert their carcinogenicity. The somatic cell mutation theory of carcinogenicity suggests that for a carcinogenic response to occur, an irreversible change must occur in the cell which results in proliferation of a neoplasm. This change reflects a mutational event in the DNA of that cell, suggesting that the chemical carcinogen must interact directly with or otherwise alter the DNA to initiate the change. In recent years, however, some substances have been shown to be carcinogenic, but by mechanisms in which there apparently is no direct interaction with or alteration of the DNA of the cell by the substance. Presumably, these compounds are not capable of initiating the alteration of a normal cell to a neoplastic one, but can facilitate expression of a neoplastic response in latent cells. On the basis of these purported differences in mechanisms, carcinogens now are often classified into two broad categories: genotoxic and epigenetic or non-genotoxic.

The mechanisms by which a compound exerts its carcinogenicity rarely can be determined by the chronic testing of whole animals such as is done in the NTP bioassay. Thus, a large number of short-term *in vitro* and *in vivo* assay systems have been developed for the purpose of elucidating mechanisms. Since most of the *in vitro* testing systems measure mutational events, and many carcinogens are mutagens, it is becoming accepted that positive results in these test systems may indicate genotoxicity. The decision as to whether a substance is genotoxic can be made qualitatively on the basis of several criteria: 1) a reliable, positive demonstration of genotoxicity in appropriate prokaryotic and eukaryotic systems *in vitro*; 2) studies on binding to DNA and 3) evidence of biochemical or biologic consequences of DNA damage (Weisburger and Williams, 1981).

No single test system appears capable of detecting all carcinogens that are genotoxic. Therefore, a number of scientists have proposed testing batteries such that results from each test within the battery, when evaluated as a whole, may allow one to make a conclusion about the mechanism of carcinogenicity of a particular compound. 1,2-Dichloroethane has not been systematically studied in any specific battery of tests, but has been evaluated in a number of test systems that have been proposed for inclusion in one or more batteries. Table V-21 lists the results obtained with 1,2-dicloroethane in a number of these short-term test systems. Each test system is designated as measuring genotoxic or nongenotoxic events. In addition, there is recorded a positive or negative result for 1,2-dichloroethane in the test system as well as the reference citation. Most of the studies have appeared in the peer-reviewed literature.

When considering the body of data as a whole, it becomes evident that 1,2-dichloroethane probably exerts its carcinogenicity primarily via genotoxic mechanism(s).

VIII. Quantification of Toxicological Effects

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Adjusted Acceptable Daily Intake (AADI) for the chemical is determined. For ingestion data, this approach is illustrated as follows:

$$\text{Adjusted ADI} = \frac{(\text{NOAEL or MEL in mg/kg})(70\ \text{kg})}{(\text{Uncertainty factor})(2\ \text{liters/day})}$$

The 70 kg adult consuming 2 liters of water per day is used as the basis for the calculations. A "no-observed-adverse-effect-level" or a "minimal-effect-level" is determined from animal toxicity data or human effects data. This level is divided by an uncertainty factor because, for these numbers which are derived from animal studies, there is no universally acceptable quantitative method to extrapolate from animals to humans, and the possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human toxicity data, an uncertainty factor is used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxins. The guidelines set forth by the National Academy of Sciences (Drinking Water and Health, Vol. 1, 1977) are used in establishing uncertainty factors. These guidelines are as follows: an uncertainty factor of 10 is used if there exist valid experimental results on ingestion by humans, an uncertainty factor of 100 is used if there exist valid results on long-term feeding studies on experimental animals, and an uncertainty factor of 1000 is used if only limited data are available.

In the quantification of carcinogenic effects, mathematical models are used to calculate the estimated excess cancer risks associated with the consumption of a chemical through the drinking water. EPA's Carcinogen Assessment Group has used the multistage model, which is linear at low doses and does not exhibit a threshold, to extrapolate from high dose animal studies to low doses of the chemical expected in the environment. This model estimates the upper bound (95% confidence limit) of the incremental excess cancer rate that would be projected at a specific exposure level for a 70 kg adult, consuming 2 liters of water per day, over a 70 year lifespan. Excess cancer risk rates also can be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. Current understanding of the biological mechanisms involved in cancer do not allow for choosing among the models. The estimates of incremental risks associated with exposure to low doses of potential carcinogens can differ by several orders of magnitude when these models are applied. The linear, non-threshold multi-stage model often gives one of the highest risk estimates per dose and thus would usually be the one most consistent with a regulatory philosophy which would avoid underestimating potential risk.

The scientific data base, which is used to support the estimating of risk rate levels as well as other scientific endeavors, has an inherent uncertainty. In addition, in many areas, there exists only limited knowledge concerning the health effects of contaminants at levels found in drinking water. Thus, the dose-response data gathered at high levels of exposure are used for extrapolation to estimate responses at levels of exposure nearer to the range in which a standard might be set. In most cases, data exist only for animals; thus, uncertainty exists when the data are extrapolated to humans. When estimating risk rate levels, several other areas of uncertainty exist such as the effect of age, sex, species and target organ of the test animals used in the experiment, as well as the exposure mode and dosing rates. Additional uncertainty exists when there is exposure to more than one contaminant due to the lack of information about possible additive, synergistic or antagonistic interactions.

Non-carcinogenic Effects

The non-carcinogenic toxic effects of 1,2-dichloroethane (1,2-DCE) in humans and other animals from both acute and longer-term exposures at relatively high levels include central nervous system (CNS) depression, liver and kidney damage, gastrointestinal distress, adrenal and pulmonary effects and circulatory disturbances. The appearance and intensity of these effects are dependent upon dose and duration of exposure. Death following high level acute exposures usually results from respiratory or circulatory failure. Delayed fatalities usually are due to renal damage. Fatty degeneration in the liver, heart and adrenals also have been observed.

No information is available on the existence of any subgroup of the human population which is likely to be more susceptible to the toxicity of 1,2-dichloroethane, nor is there any information on the nature of interaction between 1,2-DCE and other chemicals during multiple chemical exposure.

Reported minimum acute lethal doses in non-human mammals range from 600 to 2000 mg/kg (see Table VIII-1). Humans, however, may be more sensitive to the acute effects of this substance as there exists a case report describing the death of an adolescent male following ingestion of about 350 mg/kg of the solvent (Yodaiken and Babcock, 1973).

Some of the effects occurring after extended exposure in animals to 1,2-dichloroethane are described below in the section on Quantification of Non-carcinogenic Effects. Different effects were noted in rabbits exposed to 3000 ppm 1,2-DCE for 2 hr/day, 5 days/week for 90 days(Lioia and Elmino, 1959; Lioia, et al, 1959). These authors reported that the animals exhibited varying degrees of leukopenia and thrombocytopenia. In addition, there was frequent hypoplasia of the granuloblastic and erythroblastic parenchyma in the bone marrow. The cellular concentration of leukolipids was reduced, but no changes occurred in polysaccharides, peroxidase or RNA. The investigators suggested that 1,2-DCE might exert a direct poisoning effect on bone marrow.

Table VIII-1

Acute Lethal Doses of 1,2-Dichloroethane in Animals

Species	Category[a]	Dosage	Route
Mouse	LCL$_o$	5000 mg/m^3	Inhalation
	LDL$_o$	600 mg/kg	Oral
	LDL$_o$	380 mg/kg	Subcutaneous
	LDL$_o$	250 mg/kg	Intraperitoneal
Rat	LCL$_o$	1000 ppm/4 hr	Inhalation
	LDL$_o$	500 mg/kg	Subcutaneous
	LD$_{50}$	680 mg/kg	Oral
Guinea pig	LCL$_o$	1500 ppm/7 hr	Inhalation
	LDL$_o$	600 mg/kg	Intraperitoneal
Rabbit	LCL$_o$	3000 ppm/7 hr	Inhalation
	LDL$_o$	1200 mg/kg	Subcutaneous
	LD$_{50}$	860 mg/kg	Oral
Dog	LDL$_o$	2000 mg/kg	Oral
	LDL$_o$	175 mg/kg	Intravenous
Pig	LCL$_o$	3000 ppm/7 hr	Inhalation

[a] LCL$_o$: lowest published lethal concentration in air; LDL$_o$: lowest reported lethal dose by any route other than inhalation; LD$_{50}$: median lethal dose by any route other than inhalation.

Source: NIOSH, 1977, p.388

Quantification of Non-carcinogenic Effects

The only toxicological study published to date in which the test animals were exposed to 1,2-dichloroethane in their drinking water was reported by Lane, et al. (1982). The duration of dosing varied from 5 to 25 weeks, depending upon the particular protocol used. The authors conducted a multi-generation reproductive study which included screening for dominant lethal and teratogenic effects. Male and female ICR Swiss mice received the test substance at concentrations of 0, 0.03, 0.09 or 0.29 mg/l (0, 5, 15, or 50 mg/kg/day). Under the conditions of this study, there appeared to be no dose-dependent effects upon fertility, gestation, viability or lactation indices. Weight gain and pup survival were not affected adversely. No significant dominant lethal or teratogenic effects occurred in either of the two generations tested. The no-effect level of 50 mg/kg may not be the highest no-effect level since no higher doses were given. If one were to use the results of this study to derive an acceptable daily intake (ADI) for non-carcinogenic toxicity, it might be developed as follows:

$$\text{ADI:} \quad \frac{50\ \text{mg/kg/day} \times 100\%}{100 \times 10} = 0.05\ \text{mg/kg/day (or 3.5 mg/day for a 70 kg adult)}$$

Where: 50 mg/kg/day = No-observed adverse effect level (NOAEL) for reproductive and teratogenic effects

70 kg = weight of protected individual

100% = percentage of dose absorbed

100 = uncertainty factor, appropriate for use with NOAEL from animal data, and no equivalent human data

10 = uncertainty factor, for less than lifetime exposure

The study by Alumot, et al. (1976), in which 250 or 500 ppm 1,2-dichloroethane was added to the feed of rats for up to two years, yielded no significant differences between treated and control animals. Even though the authors recommended an acceptable daily intake (ADI) of 25 mg/kg, inadequacies in the conduct and reporting of the study exist, rendering this experiment inappropriate for use in the derivation of an ADI.

Longer-term inhalation exposures (up to eight months) to 100 ppm 1,2-dichloroethane for 6 to 7 hours/day, 5 days/week in a variety of animal species yielded no adverse effects as measured by general appearance, behavior, mortality rates, growth rates, organ function and blood clinical chemistry in separate studies reported by Heppel, et al., 1946, Spencer, et al., 1951 and Hofmann, et al., 1971. Exposures at higher levels (400-500 ppm) for the same duration did result in increased mortality and some pathological findings, including pulmonary congestion, diffused myocarditis, slight to moderate fatty degeneration of the liver, kidney, adrenal and heart as well as increased prothrombin time. If one were to use the NOEL of 100 ppm identified in these three studies to derive an ADI for non-carcinogenic effects, the ADI might be developed as follows:

$$\text{ADI: } \frac{405\ \text{mg/m}^3 \text{ X } 1\ \text{m}^3\text{/hr X } 6\ \text{hr X } 0.3 \text{ X } 5}{100 \text{ X } 10 \text{ X } 7} = 0.00745\ \text{mg/kg/day}$$

(or 0.521 mg/day for a 70 kg adult)

Where: $405\ \text{mg/m}^3$ = NOAEL of 100 ppm (1 ppm = $4.05\ \text{mg/m}^3$)

$1\ \text{m}^3\text{/hr}$ = respiratory rate of adult human (pulmonary rate/body weight ratio assumed to be the same for humans and test animals)

6 hours = exposure duration/day

5/7 = conversion of 5 day/week dosing to daily for 7 day/week

0.3 = fraction of test substance absorbed (assumed)

100 = uncertainty factor, appropriate for use with NOAEL from animal data and no equivalent human data

10 = uncertainty factor, for less than lifetime exposure

From the data presented above, it is obvious that alterations in reproductive function do not represent the most sensitive end point of toxicity to this substance. The end-points identified in the inhalation studies are,for now, more appropriate indicators of 1,2-dichloroethane's noncarcinogenic toxicity. Therefore, the ADI derived from this series of studies will be used to develop an Adjusted ADI for noncarcinogenic effects for 1,2-dichloroethane. Assuming that there is no exposure to 1,2-dichloroethane from other sources, the Adjusted ADI would be derived thusly:

$$\frac{7.45\ \text{ug/kg/day x } 70\ \text{kg x } 100\%}{2\ \text{l}} = 0.260\ \text{mg/l}$$

Where: 7.45 ug/kg/day = ADI for 70 kg adult

70 kg = body weight of protected individual

100% = assumed percentage contribution to total exposure by drinking water

2 l = volume of drinking water imbibed/day by 70 kg adult

The Adjusted ADI is derived to reflect allowable daily exposure of a 70 kg adult drinking two liters of water per day, and whose sole source of exposure to 1,2-dichloroethane is via that drinking water. This calculation does not reflect the associated carcinogenic risk.

Carcinogenic Effects

Near lifetime exposure to 1,2-dichloroethane has been shown to significantly increase tumor incidences at several sites in both rats and mice when administered by gavage, but not following inhalation exposures in these species (different strains) or thrice weekly intraperitoneal injections as measured by observing the incidence of lung adenomas in Strain A mice (NCI, 1978; Maltoni, et al., 1980; Theiss, et al., 1977). Negative results in the Strain A mouse system, however, are not considered to be sufficient evidence that a compound is not a carcinogen.

1,2-DCE at doses of 47 or 95 mg/kg/day was administered in corn oil by gavage five times weekly to 50 Osborne-Mendel rats of each sex per group for 78 weeks followed by an observation period of 23 weeks for males and 15 weeks for females. A statistically significant increase in the incidence of squamous cell carcinoma of the forestomach and hemangiosarcoma of the circulatory system was observed in male but not female rats ($P < 0.04$). The female rats had a significantly increased incidence of adenocarcinoma of the mammary glands ($P < 0.002$) (NCI, 1978).

In a complementary gavage study, 50 hybrid B6C3F1 mice of each sex per group were dosed five times weekly for 78 weeks with 195 or 97 mg/kg/day in corn oil for male mice and 299 or 149 mg/kg/day in corn oil for female mice. The mice were observed for 12 to 13 weeks following cessation of the treatment. A statistically significant increase in the incidence of mammary adenocarcinoma ($P < 0.04$) and endometrial stromal polyps or sarcomas ($P < 0.016$) was seen in the female mice; the incidence of alveolar/bronchiolar adenomas was increased in both sexes ($P < 0.028$) (NCI, 1978).

In an inhalation study, Swiss mice or Sprague-Dawley rats of each sex were exposed to 607.5, 202.5, 40.5, or 20.3 mg/m^3 of 1,2-DCE for 7 hours daily, 5 days per week for 78 weeks (Maltoni, et al., 1980). At the end of exposure period, the animals were allowed to live out their natural lives. In no case did the incidence of a particular type of tumor appear to be dose-related. In this interim report, the authors concluded that 1,2-DCE was not carcinogenic under the conditions of their experiment.

Several explanations have been proposed to reconcile the differences in the results of the gavage and inhalation studies. These are presented in some detail in Chapter V.

In spite of the purported inadequacies of the bioassay, NCI did conclude that under the conditions of the study, 1,2-dichloroethane was carcinogenic to Osborne-Mendel rats and to B6C3F1 mice (NCI, 1978). The National Academy of Sciences Safe Drinking Water Committee, in its updated assessment of the toxicity of 1,2-dichloroethane, recommended that additional long-term oral ingestion studies employing several species of animals be conducted to determine if 1,2-DCE is a carcinogen, and, if so, which organs are involved in different species, the nature of uptake, metabolism and accumulation of DCE and its metabolites, and minimum times and doses of DCE required to induce tumors (NAS, 1980).

On the basis of the results of the NCI bioassay, the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for 1,2-dichloroethane's carcinogenicity in test animals. For compounds classified as having sufficient evidence of carcinogenicity in animals, but lacking adequate data in humans (which would be the case for 1,2-dichloroethane), IARC states that "it is reasonable, for practical purposes, to regard such chemicals as if they presented a carcinogenic risk to humans" (IARC, 1979).

1,2-Dichloroethane was shown to be carcinogenic by the oral route, the same route by which individuals would be exposed to 1,2-dichloroethane when it is present in their drinking water. Therefore, one must determine whether or not a carcinogenic risk exists and, if so, estimate the magnitude of that risk to individuals drinking water which contains measurable levels of this substance.

1,2-DCE has been studied in a variety of short-term test systems which evaluate the mutagenic potential of the compound and/or its potential for interaction with DNA. The results of these studies are summarized in Table V-21. Positive results in certain of these test systems are considered to be predictive of carcinogenic potential.

When considering the body of data as a whole, it becomes evident that 1,2-dichloroethane possesses the potential to exert its carcinogenicity via genotoxic mechanism(s).

Quantification of Carcinogenic Effects

Using methodology described in detail elsewhere, the EPA's Carcinogen Assessment Group (CAG) has calculated estimated incremental excess cancer risks associated with exposure to 1,2-dichloroethane in ambient water, extrapolating from data obtained in the NTP Bioassay in male rats with this compound (increased incidence of hemangiosarcomas) (U.S. EPA, 1980; NCI, 1978). CAG employed a linear, non-threshold multistage model to estimate the upper bound 95% confidence limit of the excess cancer rate that would occur at a specific exposure level for a 70 kg adult, ingesting 2 liters of water and 6.5 g of fish and seafood/day ("fish factor"), every day over a 70-year lifespan.

The National Academy of Sciences (NAS, 1980) and EPA's CAG (Anderson, 1983) have estimated upper 95% confidence limit excess cancer risk rates associated with consumption of 1,2-dichloroethane via drinking water alone.

Each group used the linearized, non-threshold multistage model. NAS derived its estimates using data from the NCI bioassay showing an increased incidence of squamous cell carcinomas of the forestomach in male rats, mammary tumors in female rats and mice, endometrial tumors in female mice and lung adenomas in mice of both sexes. CAG generated its estimates based upon 1) mammary adenocarcinomas in female mice, 2) mammary adenocarcinomas in female rats, 3) squamous cell carcinomas in the forestomach of male rats, and 4) a combined risk incorporating the above three as well as the hemangiosarcomas in male rats. It is this combined risk (4)) that the ODW has chosen to represent CAG's extrapolation for drinking water.

In all three instances, a range of 1,2-dichloroethane concentrations were computed that would be estimated to increase the risk by one excess cancer per million (10^6), per one hundred thousand (10^5) and per ten thousand (10^4) in the population over a 70-year lifetime assuming daily consumption of 2 liters of water by a 70 kg adult at the stated exposure level. The ranges of concentrations and associated estimated risks are summarized in Table VIII-2.

Table VIII-2

Drinking Water Concentrations and Estimated Excess Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l)[a]		
	CAG[b]	CAG[c]	NAS[d]
10^{-4}	94	59.9	70
10^{-5}	9.4	6.0	7
10^{-6}	0.94	0.6	0.7
0	0.00	0.00	0.00

[a] Assumes the consumption of two liters of water per day by 70 kg adult over a lifetime; number represents 95% upper bound confidence limit

[b] (U.S. EPA, 1980)

[c] (Anderson, 1983)

[d] (NAS, 1980)

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